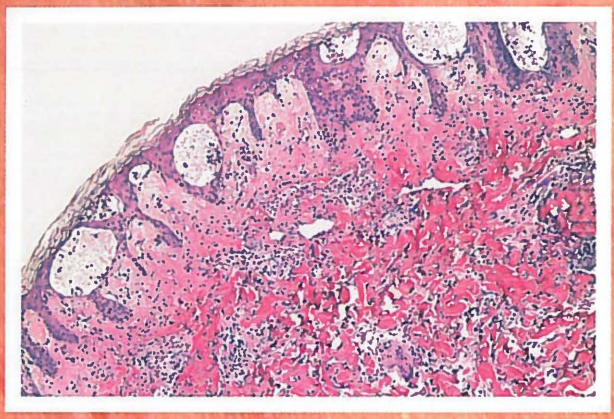
Severe cutaneous adverse drug reactions

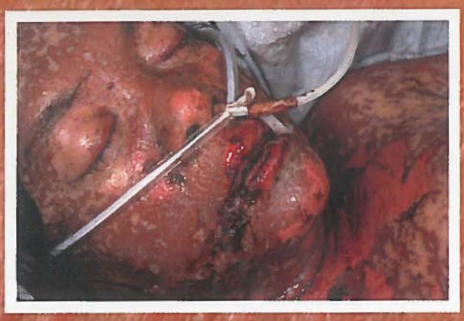
Kardaun, Sylvia Helena

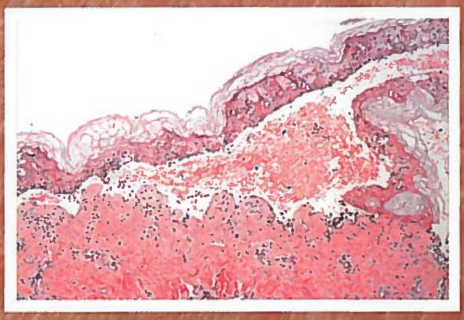


Severe cutaneous adverse drug reactions

Challenges in diagnosis and treatment

S.H. Kardaun





SEVERE CUTANEOUS ADVERSE DRUG REACTIONS

Challenges in diagnosis and treatment

Sylvia Kardaun, 2012

Stellingen behorende bij het proefschrift:

SEVERE CUTANEOUS ADVERSE DRUG REACTIONS

Challenges in diagnosis and treatment

1. Awareness of cutaneous adverse drug reactions is a prerequisite for diagnosis.

2. For most drugs, the high prevalence of medicine-related morbidity rather reflects their extensive use than their intrinsic toxic potential.

3. In cutaneous adverse drug reactions, it makes sense to isolate syndromes rather than to consider the whole as a continuum, if it helps in finding original clinical patterns, courses, causes, mechanisms and treatment.

4. The main point in dealing with Stevens-Johnson syndrome/toxic epidermal necrolysis is to restore the barrier function of the skin and mucosae as quickly as possible and in the meantime to prevent the effects of this barrier loss.

5. The general negative opinion on corticosteroids in Stevens Johnson Syndrome/toxic epidermal necrolysis is probably because they are often given too late, in too low a dose, and for too long during the process.

6. The controversy if histopathological characteristics of plaque type psoriasis can be seen in pustular psoriasis is mainly a matter of timing of the sample.

7. There are no grounds to assume that an acute pustular eruption, occurring in patients with known psoriasis, is necessarily generalized pustular psoriasis or that acute generalized exanthematous pustulosis is a variant of psoriasis.

8. A flare-up of a skin reaction during oral provocation with systemic medication on sites, implicated in previous patch testing with the same drug, possibly reflects the presence of local memory in the skin.

9. The term skin rash is a deplorable and reprehensible idiotism adored by non-dermatologists. Can you have a rash on any other organ?
(Jerome Litt)

10. More is missed by not looking than by not knowing.
(Thomas McCrae)

11. To study the phenomenon of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all.
(Sir William Osler)

12. Primum non nocere.
(Thomas Seydenham, after Hippocrates)

13. In the consulting room, evidence based medicine meets Google based medicine.

14. Eigentlich weiß man nur, wenn man wenig weiß. Mit dem Wissen wächst der Zweifel.
(Johann Wolfgang von Goethe)

Groningen, 25 juni 2012

Sylvia Kardaun

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Man reist ja nicht, um anzukommen,
sondern um zu reisen.
(Johann Wolfgang von Goethe)

Voor mijn ouders
Ed, Byrthe en Jorga

Paranimfen: Rinus Beukema
Marga Rouwhorst

CONTENTS

List of abbreviations:

ADR	Adverse drug reaction(s)
AED	Aromatic anti-epileptic drug(s)
AGEP	Acute generalised exanthematous pustulosis
BSA	Body surface area
cADR	Cutaneous adverse drug reaction(s)
CBZ	Carbamazepine
CXCL8	Neutrophil chemotactic and activating factor (Interleukin-8)
DEJ	Dermo-epidermal junction
DRESS	Drug reaction with eosinophilia and systemic symptoms
EEM	Erythema exsudativum multiforme
EEMM	Erythema exsudativum multiforme majus
EGFR	epidermal growth factor receptor
ELISA	Enzyme-linked immuno sorbent assay
(GB)FDE	(Generalised bullous) fixed drug eruption(s)
GPP	Generalised pustular psoriasis
HHV6	Human herpesvirus type 6
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HSS	Hypersensitivity syndrome
IFN-γ	Interferon-γ
IL	Interleukin
IVIG	Intravenous immunoglobulins
LE	Lupus erythematosus
LTT	Lymphocyte transformation test
NSAIDs	Nonsteroidal anti-inflammatory drugs.
p-i concept	Concept of pharmacologic interaction of drugs with immune receptors.
SCAR	Severe cutaneous adverse drug reaction
SJS	Stevens Johnson syndrome.
SJS/TEN	SJS, SJS/TEN-overlap, and TEN
SLE	Systemic lupus erythematosus
SMC	sulfamethoxazole
TCR	T cell receptor
TEN	Toxic epidermal necrolysis
TNF-α	Tumour necrosis factor α
Treg	Regulatory T cells

1

Introduction and aims of the thesis

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Introduction

It is to be expected that despite the high standards for safety and quality control on the part of pharmaceutical companies in the western world, cutaneous adverse drug reactions (cADR) cannot be prevented from occurring or even increasing in future. This is due to the rising drug consumption worldwide, and because of the introduction of new therapies for major diseases. Although all age categories can fall victim to ADR, especially the elderly are more at risk. The types of severe cutaneous adverse reactions (SCAR) studied in this thesis, Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), and drug rash with eosinophilia and systemic symptoms (DRESS), are no exception to this with an average age of over fifty years of patients, suffering from this event. Adverse drug reactions (ADR), including cADR and in particular SCAR, have a vast influence on the quality of life of patients that experience them. This makes study of mechanisms implicated and prevention an integral part of the concept of "healthy aging".

SCAR regularly presents a diagnostic challenge as several differential diagnoses have to be considered. SJS, SJS/TEN-overlap and TEN (SJS/TEN) undoubtedly constitutes the condition with the highest mortality and morbidity, also long term, while DRESS is the most complex to diagnose and presents a multitude of diagnostic traps. Although rare, the implications of SCAR can be vast; not only for the individual patient, but also for his physician, as well as for the health care system. Early diagnosis is essential to prevent unnecessary investigations and therapeutic interventions. Crucial in this respect are awareness of and knowledge on the condition at hand but also a clear case definition. Apart from early diagnosis, withdrawal of the eliciting agent, and supportive care, no evidenced treatment is currently available.

The main targets for further study of SCAR are aimed at a better understanding of the (non) immunological processes that underlie the different reaction patterns and at investigation of the genetic background and other risk factors that determine why a specific patient reacts with a specific, often "bizarre" reaction towards a drug while another one does not. This may also lead to finding better methods for testing the causality of potential suspected drugs. First results of pre-screening patients for a specific HLA-type in assessment of the potential risk for a reaction to a restricted number of drugs are promising, but up till now it is far from clear whether this will eventually lead to prevention of the majority of SCAR.

Due to the rarity of SCAR, it is difficult to create homogenous groups of patients for further study. Multinational cooperation, phenotypical standardisation and strict case definition, and validation are keys to create such groups for further analysis.

1.1 General introduction cutaneous adverse drug reactions

1.1.1 Introduction

Quality, safety and efficacy of drugs are issues of all ages. Adverse drug reactions (ADR), an inevitable consequence of drug therapy, are amongst the most important causes of iatrogenic illness in terms of morbidity and mortality, and are as old as medicine itself. The term iatrogenic from the Greek words *iatros* (healer) and *genic* (origin) nowadays reflects any adverse effect of medical or nursing care, including acts of omission.[1]

The concept of harm related to medical practice has been recognized for more than 4500 years. The ancient Egyptians had a lot of knowledge on herbal medicine and adopted an ethical code centuries before the Hippocratic Oath as shown by an inscription on the tomb of Nenkh-Sekhmet, chief of the Physicians during the 5th Dynasty (2494 to 2345 BC): "*Never did I do evil towards any person*". Homer, aware of the toxic nature of some herbs, comments in the Iliad: "there the earth, the giver of grain, bears greatest store of drugs, many that are healing when mixed, and many that are baneful; there every man is a physician, wise above human kind; for they are of the race of Paeon"[2] The leading principle in the Hippocratic Oath, originating somewhat after the 5th century BC, often cited as "*Primum non nocere*", is underlined with the statement against giving "*pharmacon oudeni*", translated as "*I will give no deadly drug*".[3] In10th century Italy, the medical school of Salerno was authorised to hang offending druggists if they had sold a poison or noxious drug. Frederic the Great (1712-1786) dictated that the life of a seller of a magic elixir or love potion would be forfeit if a purchaser died.[4]

Wouter van Doeveren (1730-1783), professor of Medicine in Groningen and first advocate of the foundation of a general hospital in this town, precursor of the current University Medical Center Groningen (UMCG), warns in his lecture "*de remedio morbo*" in 1779: "*geef niet te snel een geneesmiddel met het risico een tweede ziekte aan de bestaande ziekte toe te voegen of mogelijk de dood te versnellen*" (do not give a drug too soon, with the risk of adding a second disease to the existing one, or even to speed up death).[5]

Crucial for the development of modern pharmacovigilance was the drama with thalidomide, claimed as outstandingly safe in promotional literature. After its first marketing in 1956, large numbers of newborns with a peculiar malformation of the extremities resembling a seal's flipper (phocomelia) were noticed.[6] This resulted in national and international regulations on reporting of ADR, culminating in foundation of the drug monitoring program of the World Health Organisation (WHO) in 1967. Important in pharmacovigilance is the spontaneous frequency of an illness or symptom. If it is common (e.g. myocardial infarction in the elderly) and only rarely caused by a drug, the adverse reaction will not be readily identifiable in an observational study, unless the study is very large. On the other hand, if an illness occurs rarely (e.g. phocomelia) and a

drug causes it frequently, it may already be recognized without properly designed observational studies.[7]

In 1951, more than a decade before the thalidomide affaire, Leopold Meyler (1903-1973), published his "*Side effects of drugs*".[8] Now in its 15th edition and expanded into 6 volumes, "*Meyler's Side effects of Drugs*" is still the reference tool for ADR.[9] Initially there was a lot of criticism on Meyler and he was accused of collaborating with alternative medicine since that was "also against the use of chemicals". To his defence he stated: "*one is able to use medicines better, if next to the advantages one is also informed about their disadvantages*". Gradually he gained recognition and became professor of Clinical Pharmacology at the University of Groningen. Had his work been appreciated earlier, the thalidomide disaster might have been more limited.

In the past most drugs have been discovered either by identifying the active ingredient from traditional remedies or by serendipitous discovery. Nowadays, along increasing knowledge on diseases at the molecular and physiological level, new types of medicines are also being developed, referred to as molecular-targeted therapies and other biologicals or body response modifiers. Biologicals, closely related to substances naturally made by the body's immune system, are natural proteins such as antibodies, cytokines or fragments of proteins, or synthetic peptides that switch off specific signal proteins, thus influencing disease processes such as cancer, rheumatoid arthritis, and psoriasis. Unlike cytotoxic drugs, the interaction of molecularly targeted drugs with their target (receptor) is quite selective and can be described by the classical drug-receptor theory.[10] For targeted drugs, toxicities of conventional chemotherapeutic agents on healthy tissue, such as bone marrow suppression and mucositis, are quite rare and frequently replaced by unique and agent-specific toxicities, based on the drug's pharmacological characteristics. These side effects are usually dose related and often associated with an adverse impact on patient's quality of life.[11]

Moreover, ADR significantly hamper drug development. The number of newly marketed drugs shows a steady decline; many drugs never make it to the market because of problems already encountered in the early phase, while others are withdrawn post marketing because harm exceeds benefits.[12] Well known examples of withdrawal from the market are Softenon® (thalidomide) in the early 60's because of teratogenicity, Trancopal® (chlormezanone) in 1996 because of rare but severe cases of toxic epidermal necrolysis and Vioxx® rofecoxib in 2004 after a study showed a raised risk for heart attacks and strokes.[6,13,14]

With improved living conditions and increased life expectancy, pharmaceutical drugs have become widely consumed. Many ADR may not be severe enough to warrant admission, but can nevertheless lead to significant deterioration in quality of life or require medical assessment and treatment. Some however, do not only reduce patients' quality of life, but also represent a source of morbidity and mortality and have a major impact on public health. The high prevalence of this drug-related morbidity and mortality rather reflects extensive drug usage than an intrinsic toxic potential of particular drugs.[15]

ADR are diverse and the wide range is probably based on differences in pathomechanism. Any tissue can be the principal target, while sometimes several organ systems are involved simultaneously. The skin is one of the most common targets of ADR. Although each drug by itself is only rarely responsible, virtually every drug can provoke cutaneous adverse drug reactions (cADR). Moreover, in case of polypharmacy, it is often difficult to assign a single drug as the responsible culprit. CADR represent a diagnostic challenge for the treating physician and are easily misdiagnosed because of their huge clinical variability and heterogeneity and resemblance to idiopathic conditions. This may result in both under- and over-diagnosis. Misclassification as drug allergy may result in less effective and/or more expensive treatment, while under-diagnosis may result in even more severe reactions at subsequent re-exposure.

Dermatologists in particular will be confronted with patients with early signs of severe (muco)cutaneous adverse reactions (SCAR), requiring hospitalisation for diagnosis, stabilisation and treatment. Even though rare, SCAR have a significant impact on public health, frequently causing morbidity, mortality, lasting disability, and reluctance of patients and their physicians to subsequent use of medications.

Early recognition of ADR and the causative agent is important, looking at the potentially far-reaching consequences. Although progress has been made in improving case definitions and criteria for diagnosis and understanding of pathogenesis, especially in the last decades, better understanding of pathogenesis, improvement of case definition, including recognition of (early) symptoms, and development of effective (new) specific therapies are still needed. For balancing the risk-benefit ratio of drug prescription, improved predictability which drug candidates are likely to cause ADR and which patients are at increased risk, is important.

1.1.2 Definitions

Adverse drug events are unexpected events following drug use, without evidence of causality. In 1972, the WHO defined an ADR as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function".[16] The more recent definition: "An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product, includes the concept of error and highlights opportunities of preventive action to avoid adverse effects.[17] ADR should be distinguished from side effects, defined as "any unintended effect of a pharmaceutical product occurring at doses normally used in man that is related to the pharmacological properties of the drug". This also implies that side effects can be beneficial, sometimes even leading to new indications for prescription.

An ADR is defined as serious when it requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability, or is life-threatening. The term "severe"

is often used to describe the intensity of a medical event. The terms "severe" and "serious" when applied to ADR are technically very different. They are easily confused and should not be used interchangeably.[17]

1.1.3 Classification of Adverse Drug Reactions

In a widely used pharmacological classification, also used by the WHO, ADR are divided in 6 subtypes. Originally ADR were distinguished in dose-related and non-dose-related reactions.[18] Later, for mnemonic purposes, these were labelled respectively type A ("Augmented") and type B ("Bizarre") reactions (**Table 1**).

Type A reactions, most frequent with about 80%, are caused by the pharmacological or toxic properties of a drug. They also include drug interactions, accumulation and side effects and may occur in anyone. These reactions are predictable and dose dependent and can be diminished or alleviated by dose reduction.

Type B reactions, manifest in about 10-15% of all ADR, are presumably proportionally more frequent in cADR. The term bizarre was given because of their unpredictable and uncommon character. They occur in people with a certain predisposition, and may demonstrate a manifold of novel presentations, not to be expected from the known pharmacological properties of the medicine. Their unpredictable and serious nature makes them a significant clinical problem, also hampering drug development. Type B reactions, including both non-immunological reactions and immunologically determined hypersensitivity, are mainly dose-independent, and usually

Table 1. Pharmacologic classification of main types of ADR: type A and B

Type A predictable, common, related to the pharmacological action, low mortality

- Toxicity, overdose, accumulation	Antimetabolites (cyclophosphamide) almost invariably cause alopecia; hepatic failure with high dose acetaminophen; chrysiasis after long term gold salts
- Side effect	Sedation with antihistamines
- Secondary effect	Diarrhoea with antibiotics due to altered gastrointestinal bacterial flora, candidiasis with (broad spectrum) antibiotics
- Drug interaction	Petechiae/ecchymoses with coumarins when combined with acetylsalicylic acid

Type B unpredictable, uncommon, usually unrelated to the pharmacological action, raised mortality

- Intolerance	Tinnitus with acetylsalicylic acid
- Hypersensitivity	Immunological reaction, e.g. anaphylaxis with penicillin
- Pseudoallergy	Non-immunological urticaria with radiocontrast; NSAID intolerance
- Idiosyncratic reactions	Anemia with anti-oxidant drugs in glucose-6 phosphate dehydrogenase deficiency

require drug withdrawal for resolution. They are proportionally more severe and life-threatening than type A reactions.

Subsequently, the reaction types C (dose related and time related, "Chronic"), D (time related, "Delayed"), E (withdrawal, "End of use") and F (unexpected failure of therapy, "Failure") were added.[17-19]

Severe cutaneous adverse reactions (SCAR) can be defined in various ways but are fortunately rare. In this thesis SCAR is restricted to Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS), also known under various other names including hypersensitivity syndrome (HSS). Other severe cADR, such as anaphylaxis, serum sickness–like syndrome, and vasculitis, will not be not discussed.

1.1.4 Case definition and classification

Establishing diagnosis, reaction type, and drug causality can be challenging because of the variable clinical and biological presentation and overlap with other diseases. cADR can mimic a wide range of idiopathic dermatoses such as bacterial and viral exanthemas, neoplastic or paraneoplastic manifestations (e.g. lymphoma, leukemia, Sweet syndrome), autoimmune (blistering) and inflammatory conditions (e.g. connective tissue disease, serum sickness, Kawasaki disease), and therefore present a challenging diagnostic problem.

Clear case definition is important, not only for the patient and his treating physician, but also because it improves comparability of literature, while lack of it impairs accurate case identification and results in under- or over-diagnosis and -reporting.

Case definition and classification of cADR, as of idiopathic dermatoses, are mainly based on morphology and distribution of the (muco)cutaneous lesions. The morphology of cADR is myriad and encompasses a large variety of clinical patterns, ranging from the most common transient and benign macular or maculopapular erythema, often occurring 6–9 days after introduction of a new drug in 0 - 8 % of its users, to the most severe forms such as TEN, which fortunately are quite rare.[20,21]

Although some cases show overlap or are currently unclassifiable, it is important to recognize and distinguish the various clinical patterns, not mixing them all under the denomination of "hypersensitivity reactions" because of differences in risk factors, extra-cutaneous involvement, culprit drugs, pathogenesis, treatment, prognosis, and sequelae.[22] The estimated mortality rate for AGEP is 1-5%, for DRESS 10% and for TEN over 40%, while for the vast majority of cADR it practically is nil. In addition some medications are "usual suspects" for all reaction types, while others are more specific for a given reaction pattern. Inconsistencies in case definition can also hamper the quality of information to patients and other health care takers with potential negative future implications.

In the last decades substantial progress has been made on case definition and delineation of SCAR from other closely resembling clinical entities, including their causative drugs and other risk factors.[23-28] Unfortunately however, despite growing consensus on case definitions of SCAR, their respective criteria are not yet always strictly followed by all physicians, maintaining confusion and complicating comparison between the various studies.

1.1.5 Epidemiology

Epidemiologic data are scarce and reported numbers may be over- or underestimated. The reported incidence of the various types of ADR is amongst others influenced by definitions used, region, setting of the study population, prevailing diseases, prescription habits, and genetic differences. Results of a large meta-analysis in 1998 and later studies suggest that ADR present an important clinical issue with high mortality (4th-6th cause of death) in hospitalized patients.[29,30] Moreover, ADR frequently necessitate cessation of otherwise effective drug therapy in patients, result in hospitalization or significantly increase the length of hospital stay and costs.[31-33] Several meta-analyses and other studies have calculated that ADR account for 2.4 - 6.5% of all hospital admissions in Western countries.[29,30,32,34-37] A recent prospective, nested case control study on hospital admissions related to medication (HARM) in the Netherlands in 2006 indicates that 2.4% of all admissions and 5.6% of acute admissions are related to ADR, while 46% of these were potentially preventable.[38]

The skin belongs to the most affected organs in ADR. Skin eruptions are observed in 0.1–1% of treated patients in pre-marketing trials of most drugs. However, a number of currently used drugs are associated with higher rates of cADR, e.g. 5–7% for aminopenicillins, 3–4% for antibacterial sulfonamides and 5–10% for many antiepileptic drugs. In reported series 90% of the drug eruptions are benign.[39] Because underreporting is expected to be more frequent for benign reactions, it can be assumed that about 2% of cADR are severe.

Epidemiologic studies on SCAR are scarce and knowledge mainly relies on case reports and case series. Furthermore, reliable data on drug use of patients with SCAR as well as of the general population are needed for risk assessment. SCAR need to be well defined and separated from other conditions for assessment of the risks of a specific drug. A prerequisite for data analysis and study is consensus on case definition of SCAR. For the spectrum of SJS/TEN case definitions, already elaborated in 1993, and for AGEP a scoring system for case validation, published in 2001, are nowadays generally accepted and used.[23,24] Slightly different is the situation for DRESS, still lacking a clear case definition and consensus on nosology. Recently a proposal has been developed for case definition for HSS/DRESS, while demographics and risk factors are subject of further study.[25,28]

Very often it is quite hard to determine whether the early symptoms of SCAR, including fever or mucosal symptoms, are signs of e.g. an acute infection or the beginning of SCAR. Therefore it is crucial to determine the index day, i.e. the day of onset of the adverse reaction, since prodromes

may last for several days. Notification of prodromes is important for drug causality assessment as they are also often treated by medication.

For SJS/TEN large epidemiological studies have meanwhile provided information on incidence, demography, and also on risk factors including drugs, while for AGEP those studies exist at a smaller scale.[26,27,40,41] For DRESS, the first large series, following the newly introduced validation score system has been submitted for publication.[28]

1.1.6 Pathogenesis of hypersensitivity reactions

Drug hypersensitivity is a major clinical problem. Hypersensitivity can be defined as a "state of altered reactivity in which the body reacts with an exaggerated immune response to what is perceived as a foreign substance.[42] This definition implies unexpected, immunologically mediated reactions, and individual predisposition. Although many cADR are not immunologically mediated, including phototoxic reactions, hyperpigmentation, anticoagulant skin necrosis, toxicity towards hairs or skin of anticancer drugs, and effects on skin and appendages of corticosteroids and other hormones, there is increasing evidence that most acute cADR including SCAR are of immunological origin.[22,43]

The immune response in drug hypersensitivity is normally explained by the hapten hypothesis. It postulates that drugs with a molecular weight of less than 1000 D are too small to cause an immune response per se. However, if a chemically reactive drug or drug metabolite binds covalently to a protein and thus forms a so-called hapten-carrier complex, this modified protein can induce an immune response.[44] Many drugs that incite a delayed-type immune-mediated reaction are believed to be metabolized to a chemically reactive form or undergo bioactivation to generate haptens that are recognized by sensitized lymphocytes. The ability to detoxify reactive metabolites may be an important determinant in the development of cADR. Reactive metabolites may affect cells in various ways: they may bind to macromolecules and cause direct cellular damage, they may bind to nucleic acids and produce an altered gene product, or they may bind covalently to larger macromolecular targets, form an immunogenic complex and induce an immune response.[45,46] Growing evidence indicates that T-cell recognition of drugs is a critical step in generating hypersensitivity reactions.[47-49] T-cell activation in cADR has been evidenced in numerous studies wherein drug-specific T-cell clones have been derived from the peripheral blood of patients reacting to e.g. amoxicillin, carbamazepine (CBZ), or sulfamethoxazole (SMX).[49,50] T-cells possess clonally distributed receptors (TCR) that recognize antigen on the cell surface when presented to products of the major histocompatibility complex (MHC) genes. CD4+ T-helper cells recognize antigen presented by MHC Class II, while antigens presented by MHC Class I are recognized by CD8+ cytotoxic T-cells. This cell surface-dependent recognition is referred to as MHC-restricted antigen recognition.

The earlier mentioned hapten hypothesis has recently been supplemented by the p-i concept (or pharmacological interaction with immune receptors), which postulates that some

drugs that lack hapten characteristics can bind directly and reversibly (noncovalently) to immune receptors and thereby stimulate cells. Drugs may also bind to the MHC based on their conformation rather than their reactivity. This kind of binding, referred to as pharmacological interaction (p-i), is labile and more effective when it is on the MHC and within proximity of the T cell receptor (TCR).[46] The p-i concept has been used to explain hypersensitivity of drugs such as SMX, celecoxib, CBZ, lamotrigine, and ciprofloxacin which are not haptens/prohaptens but still elicit an immune response because their conformation allows them to fit into the MHC-TCR sandwich.[51-55]

The phenotypic diversity of cADR can be explained by engagement of a variety of cytokines and inflammatory cells and by regulatory mechanisms. For example, memory cytotoxic T-cells are key effectors in both localized blisters of (generalized) bullous fixed drug eruptions and in extensive blisters of epidermal necrolysis. This could result from distinct T-lymphocyte recruitment: $CD8^+$ cytotoxic cells largely predominate in lesions of blistering reactions (fixed drug eruption (FDE), SJS, TEN), whereas CD4+ cells predominate in "common" rashes, AGEP, and DRESS.[56] Differences in cytokine production may also contribute to different clinical features: perforin/granzyme, Fas-L, granulysin and TNF- α play an important role in SJS/TEN, interleukin 5 (IL-5) and eotaxin in DRESS, while interleukin 8 (IL-8) is important in AGEP.[57 60] Next to this, a role for regulatory T-cells (Treg) has been proposed to explain for instance the limited progression of blisters in FDE, compared to SJS/TEN.[61] The traditional classification of hypersensitivity reactions of Gell and Coombs not fully explains the various clinical features of hypersensitivity to drugs.[62,63] Most immunologically mediated type B reactions are supposedly related to delayed hypersensitivity, the phenotypic diversity of the final expression of these cADR is large. Therefore Pichler proposed a sub-classification of delayed type IV hypersensitivity reactions which seems to correspond better with the clinical heterogeneity of drug hypersensitivity (see **Table 2**), according to the cytotoxic activity of the T cells, the cytokine production and the participation of different effector cells.[64] According to this classification cytotoxicity (type IVc) from $CD4^+$ or $CD8^+$ T cells seems to participate in many drug reactions, while the final pattern is modulated by preferential activation and recruitment of monocytes (type IVa), eosinophils (type IVb) or neutrophils (type IVd).[64]

Table 2. Types of hypersensitivity reaction: mechanisms and clinical correlations

Type of hypersensitivity	Immune effector mechanisms	Clinical manifestations hypersensitivity
Immediate / anaphylactic: type I	IgE bound to surface of mast cells or basophils. Antigen-binding causes mast cell degranulation, release of histamine and other mediators	Urticaria, angioedema, anaphylaxis (insulin)
Cytotoxic: type II	Antigenic determinants on cell surfaces: targets for antibodies, either IgG or IgM. Antibodies damage cells/ tissues by activating complement, or by binding to cells through Fc receptors and activate cytotoxic killing, e.g. by NK cells	Pemphigus, blood cell cytopenias: haemolytic anaemia, neutropenia, thrombocytopenia with purpura (penicillin)
Immune complex: type III	Circulating immune complexes deposited on vascular endothelium or tissue surfaces→. complement activation & attraction of neutrophils→ tissue damage	Vasculitis, hypersensitivity vasculitis, Henoch-Schönlein purpura, Serum sickness and urticarial vasculitis (sulfonamides)
Delayed type: T-cell-mediated	T lymphocytes, ($CD4^+$ or $CD8^+$) producing different cytokine patterns and/or cytotoxic factors	Different clinical patterns e.g. contact dermatitis, exanthematous and photo-allergic reactions
Type IVa	Th1/Tc1 cells: IFN-γ, TNFα, (Il-1, Il-2) monocytes/ macrophages	Contact dermatitis, tuberculin reaction
Type IVb	Th2 cells: IL-4/-13, IL-5, eosinophils	Maculopapular rash, toxic erythema with eosinophilia, DRESS
Type IVc	Cytotoxic T cells: perforin, granzyme B, granulysin	Contact dermatitis, maculopapular rash , toxic erythema, bullous eruptions (SJS/ TEN)
Type IVd	T cells: CXCL8, GM-CSF, neutrophils	AGEP (acute generalized exanthematous pustulosis)

Drug hypersensitivity reactions, classified as type I to IV reactions according to the cytokine production, the cytotoxic activity of the T cells and the participation of different effector cells.

modified from Pichler WJ et al.[64]

1.1.7 Risk Factors

Premarketing studies are often conducted in young healthy males, neglecting factors of co-morbidities, changes in metabolism and other risk factors. Moreover, rare reactions are seldom observed premarketing due to their low incidence and the limited study population in pre-clinical trials. Hence post marketing surveillance and - studies are essential for further risk assessment.

Risk factors can be patient-related (both genetic and acquired) or drug-related. Although in most cases, factors that predispose individuals to adverse reactions with individual drugs are unknown, groups more at risk are the elderly and patients who experienced an earlier ADR, with females outweighing males.[20,33,36,65] Pharmacological, immunological and hormonal differences and the fact that women take more medications may explain some gender differences.[66,67]

Though allergic reactions are considered to be less common in the aged, because of dampening of immunological responsiveness, ADR frequently occur with increasing age, especially above 65 years. The most important determinant of risk for ADR-related hospital admissions in older patients is the number of drugs taken.[34] Age associated changes in pharmacokinetics and pharmacodynamics, altered homeostasis, multiple co-morbidities, and use of drugs with narrow therapeutic margins may also predispose the elderly.[68] Contrarily, cADR are quite rare in infants and children.[69,70] Moreover, β-lactam allergy seems clearly over diagnosed in children; the skin eruption is only rarely reproducible (6.8%) at subsequent rechallenge, and viral infections seem to be an important alternative aetiology in many of these reactions.[71]

Some co-morbidities, including infection with the human immunodeficiency virus (HIV) or infectious mononucleosis, systemic lupus erythematodes (SLE), and M. Sjögren increase the propensity for cADR.[72-80] This is amongst others demonstrated by the 10- to 50-fold increased risk for an exanthematous eruption to SMX in an advanced HIV infected patient (CD4 count <200 cells/μL).[81,82] Moreover, the importance of genetic factors has been postulated since long. These include an aberrant drug metabolism, often determined by genes encoding for drug-metabolizing enzymes and transporters, and certain human leukocyte antigen (HLA) phenotypes, which can be etnicity related. Recently several drugs have been linked to a raised risk for (c)ADR in specific HLA phenotypes.[83-87]

1.1.8 Drug causality

Assessment of drug causality in ADR is important, not only for evaluation of the benefit-risk ratio of drugs in pharmacovigilance, but also for management of the reaction and prevention of future reactions in a specific patient. Timely recognition of the culprit is of eminent importance in SCAR; prompt withdrawal of the culprit within the first 24 hours after the start of blistering for example lowers the rate of mortality in SJS/TEN.[88]

Key in assessment of drug causality is a thorough evaluation of the temporal relation of drug intake to onset of the ADR. The use of flow sheets documenting symptoms, drugs and dates can be very helpful. Consideration must be given to the likelihood according to literature of a particular drug to cause the symptoms, particularly in case of polypharmacy. Naranjo *et al.* devised an algorithm to assess drug culpability, leading to a score of probability (**Table 3**).[89] Although of limited value because the algorithm has not been validated, it mentions important points of attention when assessing drug causality. Another regularly used method for determining the causal relationship between a potential causative drug and the adverse reaction, "doing it the French way", is adapted from Begaud *et al.*[90,91]

1.1.9 Diagnostic Tests

Rechallenge tests, including re-administration of a small test dose of the suspected culprit to determine the causative drug, should not be undertaken in severe cADR as they may result in a quick recurrence of signs and symptoms and even near-fatal reactions.[92] Other in vivo and in vitro tests with the suspected drugs may be of use to confirm diagnosis and to assign the culprit, although these tests are still not routinely conducted because they can be time-consuming and complex. Sensitivity and specificity are variable, depending on the drug, type of cADR, and

Table 3. Naranjo causality scale for adverse drug reactions

Question:	Yes	No	Unknown
1. Are there previous conclusive reports on this reaction?	1	0	0
2. Did the adverse event appear after the suspected drug was given?	2	-1	0
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	1	0	0
4. Did the adverse reaction reappear when the drug was readministered?	2	-1	0
5. Is there an alternative explanation/cause that could have caused the reaction?	-1	2	0
6. Did the reaction reappear when a placebo was given?	-1	1	0
7. Was the drug detected in any body fluid in toxic concentrations?	1	0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0
10. Was the adverse event confirmed by any objective evidence?	1	0	0

Scoring > 9 = definite, 5-8 = probable, 1-4 = possible, 0 = doubtful ADR.

Naranjo et al.[89]

timing of the test, while testing should most often only be performed when the reaction has already subsided.[93-95]

Santiago *et al.* observed positive patch test reactions in 32.1% of DRESS cases, most often concerning aromatic antiepileptic drugs (AED), in particular CBZ.[96] On the other hand, Wolkenstein *et al.* have shown that sensitivity of patch testing is extremely low in SJS/TEN, as only two of 22 tested patients had a relevant positive patch test, whereas positive patch tests are proportionally overrepresented in AGEP.[97,98]

Currently the focus of allergological testing has shifted to ex vivo/in vitro tests. Only few studies are available regarding the sensitivity of the lymphocyte transformation test (LTT) that measures the proliferation of T cells to a drug in peripheral blood mononuclear cells; some authors report frequent positive test results.[95,99] Test results can be markedly influenced by their timing, which seems to be reaction specific. Actually, in several cases a positive LTT was not obtained until 3 months after onset of the disease in cases of DRESS.[95,100] Unfortunately, the sensitivity of the LTT is still very low in SJS/TEN, even when performed within the reaction specific optimal window of one week after onset of the disease.[95] Measuring a panel of inflammatory cytokines, especially IL-5, instead of proliferated lymphocytes by means of flow cytometry, the enzyme-linked immuno sorbent assay (ELISA) test, or a combination of both, might increase the sensitivity of the LTT in general.[99,101,102] Another recently reported approach evaluates up-regulation of CD69 on T-lymphocytes, two days after lymphocyte stimulation in vitro, as a sign of drug hypersensitivity.[103] Novel other in vitro methods, e.g. detection of CD 107a upregulation with or without Il-7/15 preincubation, to help to identify the culprit in drug allergic patients, are still under development.[104]

For cases in which toxic metabolites are involved, the in vitro lymphocyte toxicity assay with the suspected drug(s) could provide an additional diagnostic tool as it helps to increase the accuracy of causality assessment of the likely agent. Additionally it could serve as a screening test for potential 'cross-reacting' drugs by measuring the lymphocyte phenotypic detoxification systems.[105,106]

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1.2 Stevens-Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN)

1.2.1 Introduction

Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe ADR characterised by massive epidermal necrosis.[1-3] Even though rare, they have a significant impact on public health because of high mortality (20-25% overall and over 40% in TEN), frequent lasting disability, and reluctance of survivors and their physicians to subsequent use of medications.[4,5] While in the past, erythema exsudativum multiforme (EEM), SJS, and TEN were regarded diseases belonging to the same spectrum, SJS, SJS/TEN-overlap, and TEN (SJS/TEN) are nowadays considered to represent a single disease, whereas EEM is a different entity.

EEM has been reported under a variety of labels and eponyms, and is surrounded by confusion. The original description of this polymorphous erythema is ascribed to the Austrian dermatologist Ferdinand Von Hebra in his publication of the "Atlas der Hautkrankheiten" in 1860.[6] He described EEM as "a mild illness causing the sudden onset of many red papules that are recurrent in some patients, due to systemic invasion by some unknown factors". Some of these papules develop into what Von Hebra named "target" or "iris" lesions.

In 1922, the American paediatricians Stevens and Johnson reported severe oral involvement, conjunctivitis, and skin lesions in two boys. EEM was excluded as diagnosis because of a variety of symptoms that didn't fit Von Hebra's description of EEM. Moreover, skin lesions were more severe than the papules associated with EEM, showing terminal heavy crusting, and the patients had subjective symptoms with high fever. Stevens and Johnson believed the disorder to be an infection of unknown origin.[7]

In 1950 Bernard Thomas distinguished EEM minus, the entity as previously described by von Hebra, from EEM majus (EEMM), showing in addition bullous lesions and intensive mucosal involvement as can be seen in SJS.[8] This subdivision resulted in a lot of confusion between EEM and SJS: although the cases reported by Stevens and Johnson in 1922 differed in many aspects from EEMM, the terms EEMM and SJS became used interchangeably or as synonyms.

After an earlier description of "erythroderma with epidermolysis" by Debré *et al.* in 1939, Alan Lyell reported four cases with very extensive "epidermal necrolysis", distinct from EEM or SJS and believed to be of toxic origin, for which he coined the term "toxic epidermal necrolysis" in 1956.[9,10] Included in these four was one case of adult staphylococcal scalded skin syndrome (SSSS), leading to two decades of confusion with overlapping nomenclature for SSSS and TEN, such as staphylococcal-induced toxic epidermal necrolysis and drug-induced scalded skin syndrome. Moreover, one of the other cases in his original series was later on considered to have had generalized bullous fixed drug eruption. Although TEN is a meaningful acronym, the terms epidermolysis acuta toxica, M. Lyell or Lyell's disease are also still in use by some.

Table 1. Differences between erythema exsudativum multiforme majus (EEMM), Stevens-Johnson-syndrome (SJS), toxic epidermal necrolysis (TEN) and SJS/TEN-overlap syndrome

Clinical entity	EEM majus	SJS	SJS/TEN overlap	*TEN
Primary lesions	Typical or raised atypical target lesions	Flat atypical target lesions, erythematous/ purpuric maculae	Flat atypical target lesions, poorly defined erythematous/ purpuric maculae	Flat atypical target lesions, poorly defined (dusky) erythema
Distribution	Isolated lesions, localised, mainly acral	Isolated lesions, partly confluent, widespread +	Isolated lesions, partly confluent, widespread ++	Isolated lesions, partly confluent, widespread +++
Mucosae ≥ 2	Often	Generally	Generally	Generally
Systemic symptoms	Minimal/ absent	Usual	Always	Always
Detached body surface area (BSA)	< 10%	< 10%	10-30%	≥ 30%*

* NB: including TEN with large confluent erythema without discrete lesions with a detached BSA ≥10%
+ = mild, ++ = moderate, +++ = severe

The EuroSCAR study group proposed a consensus on case definition, classification and nosology, recognizing five categories varying from EEMM to TEN (**Table I**) in 1993.[1] This classification is based on three clinical criteria: pattern of the individual lesions, distribution, and extent of detachment. Important for differentiation of EEMM and SJS/TEN are the individual pattern and distribution of skin lesions. EEMM is characterized by mainly acrally distributed "typical targets" or "raised atypical targets" fitting the original description of EEM by Von Hebra, and epidermal detachment < 10% of the body surface area (BSA). In SJS/TEN on the other hand, skin lesions are widespread and show blisters arising on erythematous or purpuric macules and/or flat atypical targets, closely resembling the original description of SJS and TEN. Mucous membrane erosions can be present in both EEMM and SJS/TEN. Besides, EEMM significantly differs from SJS/TEN by occurrence in younger males, frequent recurrences, less fever, milder mucosal lesions, and lack of association with collagen vascular diseases, human immunodeficiency virus infection, cancer, and drug aetiology.[11] SJS/TEN is considered a spectrum of severity variants of a single disease based on similar pathogenesis, risk factors and causality. The principal difference between SJS and TEN is the extent of detachment, while SJS can progress into TEN.

Although this consensus on case definition and nosology is generally accepted nowadays, confusion can still regularly be met in literature, even in some textbooks. This hampers

comparison of literature on clinical and histopathological aspects, risk factors including drug causality, prognosis and therapy.

1.2.2 Epidemiology

The incidence of SJS is estimated at 1.2-6.0 per million per year and that of TEN at 0.4-1.2 per million per year in Europeans.[2,4,12,13] The mean age for SJS/TEN ranks between 48.2 years and 53.4 years (range 1-98), and a female preponderance of around 60% is observed.[5,14]

1.2.3 Clinical characteristics

The onset of SJS/TEN is abrupt. Prodromes, usually starting as flu-like symptoms with fever, sore throat, rhinorrhea, anorexia and malaise, are often followed by erosive stomatitis and eye involvement.[15]

Next, painful and often ill defined erythematous and/or purpuric maculae (spots) and atypical target lesions occur. Maculae, sometimes slightly infiltrated, frequently start on the face, neck, and upper trunk in a symmetrical distribution, extend proximally, and have a tendency to rapid coalescence. Most often within 24 hours extensive mucocutaneous blistering and detachment on an erythematous base is developing, a process that may last for about up to 15 days. Blisters are flaccid and can become confluent, while large sheets of epidermis slough off, leaving an exposed, weeping dermis and leading to large areas of detachment. At gentle pressure, blisters can often be moved laterally due to detachment of the blister from the dermis. This phenomenon is often referred to as "a positive Nikolsky sign" (Nikolsky II) or Asboe Hansen sign. Also pressure on erythematous skin may cause detachment (often called "a positive Nikolsky sign" or pseudo-Nikolsky sign).[16] Total detachment of BSA is often less extensive than the area of erythema, and the moment of maximal detachment is regarded to present the full blown stage of the disease.

Target lesions in SJS/TEN are atypical and differ from typical target lesions in EEM(M). Typical targets have regular round and well-defined borders with at least 3 different concentric zones: a purpuric central disk with or without a blister, a raised oedematous, pale intermediate ring, and an erythematous outer ring. (**Fig. 1a,b,c**) By contrast, raised and flat atypical targets have an appearance reminiscent of targets, but present with only 2 zones and/or a poorly defined border, while the centre can be vesicular or bullous; a central blister however is not enough to classify a lesion as raised (**Fig. 1d,2a**).

In SJS, maculae, atypical target lesions, small blisters and small areas of detachment are most often predominant on the upper chest. Maculae have a more purpuric component and are often more defined compared with SJS/TEN-overlap and TEN (**Fig. 2b,c,d**). Although these boundaries are rather artificial, total detachment in SJS is < 10% of the BSA, in SJS/TEN-overlap between 10% and 30% (**Fig. 3a,b,c,d**), whereas in TEN detachment is over 30% (**Fig. 4a,b,c,d**). TEN is also

defined in case of presence of large confluent erythema without spots with a detachment of ≥10% of the total BSA.

Multiple mucosal membranes are generally affected in SJS/TEN, with haemorrhagic blistering and erosions (**Fig. 2c,d**). Significant involvement of mucous membranes includes oral, ocular, nasal, urethral and vaginal mucosae, while tracheobronchial and gastrointestinal mucosae can also be affected.

Visceral involvement, especially of the liver has been reported.[17-19] Anaemia and lymphopenia are frequent, while neutropenia often predicts bad prognosis.

Complete healing, especially in TEN, can last 3-6 weeks; hospitalization for TEN generally takes longer than for SJS.[2,20] The period of re-epithelialisation in SJS/TEN is variable and typically takes 1-3 weeks, but especially erosions on the back, buttocks, and mucosae often take longer to heal; lesions on the glans penis for example can persist up to 2 months.[21] Herpes simplex can be a complicating factor, sometimes responsible for unexpected worsening and/or delayed healing of (muco)cutaneous symptoms.[22]

1.2.4 Prognosis/sequelae

Mortality rates differ for the diverse entities with virtually no death in EEM, 1% in EEMM and about 10% in SJS, 30% in SJS/TEN overlap and over 40% in TEN.[4,11,23,24] Multi-organ failure (particularly cardiovascular), metabolic failures, and septicaemia (often caused by Staphylococcus aureus or Pseudomonas aeruginosa) following loss of epidermal integrity are the most important causes of death. The mortality rate of SJS/TEN remains high and even seems to increase over the years despite advances in early diagnosis and management.

Important prognostic factors are age, extent of denuded skin, neutropenia, serum urea nitrogen level, and visceral involvement. Involvement of mucosae of airways and the gastrointestinal tract often indicates an unfavourable prognosis.[25,26] Culprit drugs with long half-lives are more likely to result in a fatal outcome than those with short half-lives.[27]

In 2000 SCORTEN, a validated, prognostic severity-of-illness score for SJS/TEN, predicting in hospital mortality, was developed. This mathematical tool is based on seven independently predicting clinico-biologic risk factors, including age, recent malignancy, percentage detached skin, tachycardia, and serum urea, glucose and bicarbonate levels (**Table 2**). The number of risk factors progressively attributes to the predicted mortality rate (**Table 3**).[28] The score has also been found useful for comparison of different studies and evaluation of efficacy of therapeutic interventions.[22,29-31] Due to lacking laboratory data, this score is not always applicable. Recently a simplified score yielding comparable results has been proposed, which is especially useful for evaluating retrospective cases and for settings with limited laboratory facilities. In this model, the auxiliary score, laboratory parameters are no longer included.[23]

In SJS/TEN, late sequelae are encountered in the majority of patients. Although (muco) cutaneous healing usually is complete, mucosal scarring may result in strictures with

Table 2. SCORTEN

Independent prognosis factors		Weight
Age	≥ 40 years	1
Malignancy*	Yes	1
Body surface area detached	≥ 10%	1
Tachycardia	≥ 120/min	1
Serum urea	> 10 mmol/l	1
Serum glucose	> 14 mmol/l	1
Serum bicarbonate	< 20 mmol/l	1
SCORTEN		7

* Recent cancer and haematological malignancies

Presence of variable parameter is scored as 1, its absence scored as 0. The sum total of all individual scores predicts the risk of mortality.

Table 3. Mortality rates and relative risks according to SCORTEN

SCORTEN	Mortality rate		Odds ratio (95% CI [a])
	Percent	95% CI	
0–1	3.2	(0.1–16.7)	1
2	12.1	(5.4–22.5)	4.1 (0.5–35.2)
3	35.3	(19.8–53.5)	14.6 (2.0–138.0)
4	58.3	(36.6–77.9)	42.0 (4.8–367.0)
5	90.0	(55.5–99.8)	270.0 (15.0–487.0)

[a] Confidence interval.

functional impairment. Also known are for example tooth problems including caries, nail loss, cutaneous scarring, dry skin, hypohidrosis, and pigment abnormalities (**Fig. 5a**), especially hypopigmentation.

Much more frequent and chronic than initially presumed are eye complications (**Fig. 4d**). Residual potentially disabling lesions do occur in over half the of SJS/TEN (**Fig. 5b**).[32] Serious late ocular complications are not restricted to cases with severe acute ocular involvement and care should be taken, even in mild cases. Loss of corneal epithelial stem cells during the acute stage due to severe ocular surface inflammation results in conjunctivalisation and vascularisation on the cornea, leading to serious visual impairment. Cicatrisation of conjunctival erosions may lead to inverted eyelashes, photophobia, burning or watery eyes, a sicca-like syndrome, and corneal and conjunctival neovascularisation.

Also after discharge, extended care is needed for ophthalmologic and other mucous membrane sequelae like oesophageal, urethral, penile, vaginal and anal strictures/scarring and respiratory failure due to tracheobronchial shedding.

1.2.5 Histopathology

Early lesions most often show sparse superficial perivascular and interstitial lymphocytic infiltrates, some lymphocytes at the dermo-epidermal junction (DEJ), and widespread keratinocyte apoptosis scattered throughout the lower epidermis (**Fig. 6a**). Additionally, in fully developed lesions, subepidermal vesiculation appears secondary to extensive presence of necrotic keratinocytes, which may result in full-thickness epidermal necrosis and separation at the DEJ (**Fig. 6a,b**). Sometimes, the upper infundibulae and eccrine ducts can be involved as well. The cornified layer retains its basket-weave pattern.[33] Biopsies, taken at a later phase, may complicate diagnosis by showing secondary changes.

Whereas blister fluid cells mainly contain lymphocytes, immunohistochemical staining of the skin from TEN patients shows predominance of cells of the monocyte-macrophage lineage with variable numbers of $CD8^+$ lymphocytes and macrophages in the epidermis and $CD4^+$ lymphocytes in the papillary dermis, with TNF-α as a major cytokine. Paquet *et al.* showed that macrophages are the most numerous cells in the epidermis, while factor $XIIIa^+$ dendritic cells are abundant in the dermis.[34]

For rapid differentiation of SSSS from SJS/TEN, a frozen section of a biopsy or of peeled skin can be analyzed. The level of skin cleavage in SSSS is the epidermal granular cell layer, whereas in SJS/TEN full-thickness epidermal necrosis is seen together with subepidermal blistering (**Fig. 6c**).

1.2.6 Differential diagnosis

Although diagnosis of SJS/TEN usually is obvious, based on history and clinical presentation, histopathology and immunofluorescence studies may be needed to exclude other (immuno) bullous diseases, particularly in the early stage when the full-blown clinical picture is not yet apparent.

It is important to differentiate SJS/TEN from exfoliative dermatitis and blistering diseases, in particular EEMM (**Fig. 7a**), GFBDE (**Fig. 7b**), graft versus host disease (GvHD) (**Fig. 7c**), second degree burns (**Fig. 7d**), non-specific bullous drug reactions (**Fig. 7e**), AGEP, DRESS, and SSSS (**Fig. 7f**). Also (bullous) autoimmune dermatoses such as (paraneoplastic) pemphigus (**Fig. 7g,h**), pemphigoid, linear IgA disease, and (systemic) lupus erythematosus/ (drug induced) subacute cutaneous lupus erythematosus (**Fig. 7i,j,k**) have to be considered.

Clear overlap of SJS/TEN with AGEP and DRESS, although increasingly reported, is probably more exceptional then sometimes assumed. A supposed overlap of AGEP and SJS/TEN can often be attributed to confluence of pustules in AGEP, leading to a "positive Nikolsky sign" and superficial blistering resembling TEN. Histopathology can be of help in the differentiation of these cases.[35-37] SJS/TEN may suggest overlap with DRESS when accompanied by visceral involvement, most often of liver or lungs. Most important for differentiation, is a strict application of their respective case definitions.[1,38,39]

1.2.7 Diagnostic Tests

Patch testing is an investigational option, but sensitivity is relatively weak in SJS/TEN; in one study only two of 22 cases had a relevant positive test.[40,41] The lymphocyte transformation test (LTT) can also help to determine the offending drug, although it is time consuming and its sensitivity also is rather low in SJS/TEN, compared to other cADR.[42] Crucial for the LTT appears to be the time of testing, which can vary, depending on the type of cADR. According to one study it should be performed within 1 week after the onset of the eruption in patients with SJS/TEN.[43]

1.2.8 Pathogenesis

Pathogenesis is not yet fully elucidated and controversial; several mechanisms have been postulated. Although no mechanism has been definitely proven, SJS/TEN is nowadays considered to represent an immune-mediated process in which an inappropriate immune activation is triggered in response to certain drugs or their metabolites and in which massive keratinocyte apoptosis is the main feature and cytotoxic T cells are the main effector cells. The link between drugs and the apoptosis of keratinocytes has been established by demonstrating the presence of drug-specific cytotoxic memory T cells within the skin lesions. Activated drug-specific cytotoxic T-cells have been demonstrated in lesional skin with $CD8^+$ T-cells in the epidermis and $CD4^+$ T-cells in the dermis. Drug specific $CD8^+$ cytotoxic lymphocytes in the epidermis and early blister fluid possess natural killer activity and probably kill keratinocytes by direct contact.[44] Apart from immunologic mediated mechanisms, provoked by the inciting agent, clonal expansion of cytotoxic T lymphocytes together with mononuclear cells induce apoptosis in keratinocytes, resulting in splitting and detachment of large parts of the skin at the DEJ.

Massive apoptosis of keratinocytes in SJS/TEN has been explained by an altered ability to metabolize the offending drug in some patients. This may cause formation of reactive metabolites that bind to and alter cell proteins, triggering a T-cell–mediated cytotoxic reaction to drug antigens in keratinocytes.[45,46] Some drugs may impair detoxification pathways resulting in the production of reactive oxygen species, which can be also involved in the etiology of SJS/TEN. These chemically reactive molecules may cause damage to the intracellular machinery and membranes and trigger pro-apoptotic processes including FasL expression and inflammatory cytokine production such as TNF-α.[47] Moreover, patients with sulfonamide-induced TEN are usually slow acetylators.[48-50]

Cytotoxic T cells can activate the caspase cascade, inducing apoptosis either through the Fas-Fas ligand (FasL) or the perforin/granzyme B pathway, which is responsible for keratinocyte death in SJS/TEN.[44,51,52] It has been suggested that there is an increased rate of keratinocyte apoptosis in lesional skin of patients due to increased expression of keratinocyte membrane bound Fas and FasL. Binding of the suicide antigen Fas (CD95) to its ligand (FasL, CD95L) induces downstream signalling for triggering apoptosis.[51] Later studies however contradict a crucial

role of Fas-FasL interaction or perforin and granzyme B, because both pathways seem not to be specific for SJS/TEN.[53]

Recent findings suggest that granulysin, a powerful pro-inflammatory cytotoxic protein released from cytotoxic T lymphocytes and natural killer (NK) cells, also "turns on" extensive keratinocyte apoptosis (**Fig. 8**), also highlighting a mechanism for cytotoxic T cell- or NK cell-mediated cytotoxicity that does not require direct cellular contact.[54] Granulysin concentrations in SJS/TEN blister fluids were two to four times higher than those of perforin, granzyme B or soluble Fas ligand. Moreover, depletion of granulysin reduced cytotoxicity, whereas injection of granulysin into mouse skin resulted in SJS/TEN mimicking features.[54] It was suggested that an increasing serum level of granulysin could serve as an early diagnostic biomarker for SJS/TEN.[55]

Cytotoxic T cells however, are not solely responsible for the massive apoptosis, considering e.g. the relative paucity of infiltrating cells compared to the diffuse epidermal apoptosis.[56] Drug-specific cytotoxic T cells secrete large amounts of IFN-γ initiating the MHC-restricted lysis of keratinocytes involving perforin and granzyme B. IFN-γ on the other hand also promotes the recruitment and activation of macrophages, monocytes and dendritic cells. These cells in turn produce other proinflammatory cytokines such as the soluble death factors TRAIL (TNF-related

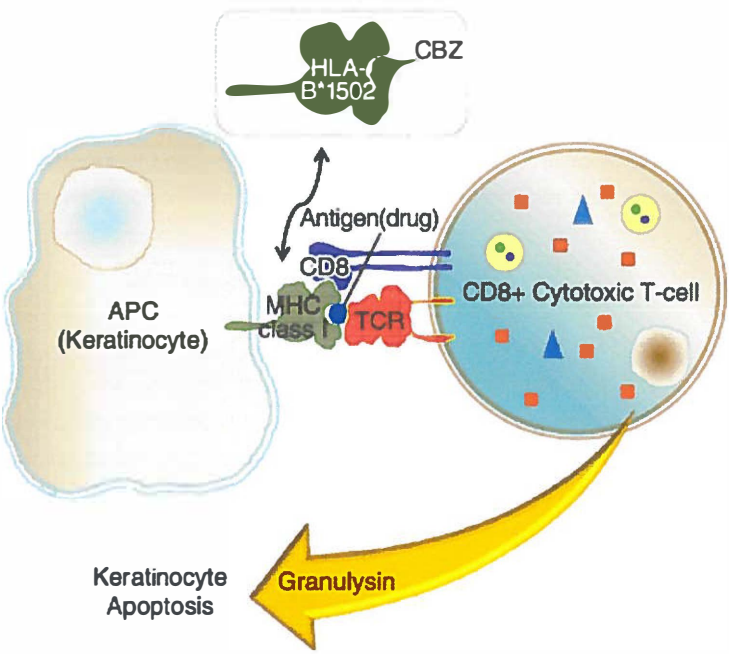

Figure 8: Model of keratinocyte apoptosis induced by the immune synapse of drug HLA - T cell receptor interaction of CD8+ cytotoxic T cells.

Wen-Hung Chung and Shuen-Iu Hung.
Genetic Markers and Danger Signals in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis.
Allergology International 2010; 59: 325-332.

apoptosis-inducing ligand), TWEAK (TNF-related weak apoptosis inducer) and possibly other cytokines. TNF-α derived from macrophages and keratinocytes may also play a role by inducing apoptosis of epidermal cells or by attracting cytotoxic effector cells, including cytotoxic T- and NK cells. [56] Moreover, upregulation of innate immune cells and molecules such as macrophages, dendritic cells, and α-defensins in T cells from patients with SJS/TEN may also be involved in the etiopathology. [57] This process culminates in a cooperative keratinocyte killing process through an MHC dependent pathway. The aggressive epidermal destruction in TEN and probably also the progression from SJS to TEN occurs in conjunction with amplification mechanisms that are not yet all elucidated. In particular the role of cytotoxic CD8+ cells in initiating the phenomenon, of regulary T cells (Treg cells) controlling the response, and of dendritic cells and monocytes should be further addressed.[58] A role for defective Treg cells has been proposed.[58,59] Treg cells present in normal numbers but functionally ineffective in the acute stage of TEN, regain their function at disease resolution.[58] Following an initial apoptotic stimulus, it is likely that apoptotic signals are amplified by cytokines. The massive release of (proinflammatory) cytokines by activated mononuclear cells and keratinocytes into the systemic circulation can induce metabolic imbalance, multiorgan failure, pulmonary embolism, and gastrointestinal haemorrhage, and besides contribute to local cell death, fever, and malaise.[21]

A genetic predisposition is probably of importance.[60] The immune reaction in SJS/TEN is proposed to be initiated by a HLA class I-restricted presentation of antigens (drugs or their metabolites) to T lymphocytes. The important role of HLA-B in the pathogenesis of cADR has been demonstrated before, although the exact mechanism of how the antigen modulates cytotoxic activity via the HLA gene is still poorly understood.

1.2.9 Risk factors

SJS/TEN nearly always represents an idiosyncratic reaction to medication, although incidentally, SJS/TEN has also been reported after vaccinations and exposure to chemicals and fumigants.[61-63] The reaction is not dose-dependent and latency time is shorter after drug reintroduction. Recent or recurrent herpes, the principal risk factor for EEM(M), has a small but still significant role in the aetiology of SJS, but not in SJS/TEN-overlap or TEN.[11,64-67] Also infection by Mycoplasma pneumoniae, regularly found in EEM(M), is quite rare in SJS/TEN.[11]

A relatively higher prevalence of connective tissue disease, HIV, but also of cancer, was confirmed in a case control study, while a recent study has shown that patients with lupus are considerably overrepresented in SJS/TEN.[68,69] An increased risk for TEN in patients with AIDS might be explained by the large number of drugs administered to these patients, the altered immune system function, and the possible abnormal pattern of production and detoxification of drug metabolites.

The association of SJS/TEN with drug-specific HLA antigens has been emphasized recently: HLA-B*1502 is strongly associated with CBZ-, and HLA-B*5801 with allopurinol-induced SJS/TEN

in patients of Southeast Asian ancestry, especially in Han Chinese.[70-77] These "markers" can be used for pretreatment screening in high risk populations. The sensitivity and specificity of the HLA-B*5801 allele for prediction of allopurinol-induced SJS/TEN in the Thai for instance were 100 and 87% respectively, suggesting that HLA-B*5801 is a valid genetic marker for screening.[78]

Moreover this type of drug reactions is more commonly seen in slow drug metabolizers due to a genetic polymorphism. Polymorphism is observed in position 308 and 328 of the promoter region of the TNF- α gene in CBZ hypersensitivity.[79]

1.2.10 Drug causality

The offending drugs for SJS and TEN do not differ. The risks of SJS/TEN related to medication was first assessed in a case-control study (SCAR-study) in 1995.[80] Although more than 100 different causative drugs have been described, high relative risks (RR) were observed for anti-infective sulfonamides (especially co-trimoxazole), CBZ, phenytoin, phenobarbital, non-steroidal anti-inflammatory drugs (NSAIDs) of the oxicam type, allopurinol, chlormezanone, aminopenicillins, cephalosporins, quinolones, and cycline antibiotics.[80] Among medication more recently introduced into the market nevirapine and lamotrigine were highly associated with SJS/TEN.[68] A lower but still significant RR was found for sertraline, while for other medications with prior alerts, such as terbinafine, fluconazole, cyclooxygenase 2 inhibitors, and leflunomide, numbers of exposed cases and controls were too small for risk assessment.[68] However, since SJS and TEN are rare conditions absolute risks remain low, even for drugs with a high RR.

SJS/TEN occur in 1 to 10 per 10,000 new users of older AED, especially CBZ, and 2.5 per 10,000 new users of lamotrigine, a newer class of anticonvulsants, 90% of which within the first 63 days after its initiation. Sodium valproate and other newer anticonvulsants rarely cause cADR. Therefore, AED should be used cautiously and especially when used for pain management, safer alternatives should be considered.[81]

Allopurinol is the most common cause of SJS and TEN in Europe and Israel; besides a raised risk was found with daily dosages of 200 mg or more.[82] Halevy *et al.* did not find an increased risk in case of co-medication with diuretics, aminopenicillins, angiotensin converting enzyme inhibitors, acetylsalicylic acid or diclofenac.[82] Noteworthy, allopurinol was often administered for asymptomatic hyperuricemia in these cases. Since other studies also revealed inappropriate indications for allopurinol in up to 86% of patients, judicious prescription of allopurinol is recommended.[83,84]

In SJS/TEN, a latency of 4-28 days (mean 12-14 days) is the most suggestive timing to support drug causality. However, this period can be up to 8 weeks for AED.[68,85] Recently, a new algorithm of drug causality for epidermal necrolysis (ALDEN) was proposed for assessing drug causality in SJS/TEN. Based on case-control data from the EuroSCAR study, ALDEN pointed to a "probable" or "very probable" causality in 69% of cases compared to 23% with the French method ($P < 0.001$),

while it scored a "very unlikely" causality for 64% of medication compared to none with the French method.[86,87]

Because of potential recurrences, patients must avoid any future exposure to the agents that were implicated in SJS/TEN; accidental rechallenge with a small amount of the culprit drug has led to fatal TEN.[88]

1.2.11 Management and treatment

Patients with SJS and TEN are usually hospitalised for observation and treatment. Treatment of SJS/TEN is highly specialized and requires specific expertise and facilities. First line of treatment is cessation of the suspected culprit drug. In case of doubt, preferably all medication, especially those started the month before the event, should be stopped. For drugs with short half lives prompt cessation has a positive effect on the outcome and lowers mortality.[27]

Attempts have been made to decrease mortality by improved supportive care and several modalities of specific treatment, but apart from direct withdrawal of the culprit and intensive supportive care, generally accepted guidelines for specific treatment are lacking. Restoring the barrier function of skin and mucosae as quickly as possible and in the meantime preventing negative effects of its loss is of eminent importance.[22,89]

Intensive monitoring includes evaluation of SCORTEN and vital parameters (blood pressure, body temperature, respiratory and heart rate, oxygen saturation), laboratory investigations (blood count, electrolytes, renal-, liver function, blood gases, bicarbonate, glucose, blood culture, urine analysis), skin cultures (bacterial swabs), and BSA involvement. To protect patients from infection, nursing has to be barrier protected. Because of massive loss of body temperature and fluid through the skin, the patient is preferably treated on an "air-fluidized" bed in a temperature and moisture regulated room with, for aseptic reasons, a laminar down flow stream. The hypercatabolic state induced by SJS/TEN demands nutritional correction to support the process of healing. Enteral feeding should be instituted early and the parenteral way should only be used when enteral feeding is impossible. The fluid balance should be monitored regularly, combined with timely supplementation of fluid, and electrolytes.[89]

Extensive wound care includes emollients, local antibiotics, and non adhesive hydrocolloid dressings. Antibiotics, pain treatment and sedatives are given as needed.[22,90] Removing only epidermis that is curled up is preferred over debridement of all detachable epidermis - a procedure in many burn centres - to support regeneration of the skin. Painful involvement of mucous membranes (oropharynx, eyes, genitalia and anus) requires attentive nursing care. The tracheobronchial epithelium and, less often, gastrointestinal epithelium can also be affected, causing high morbidity and mortality.

Besides optimal supportive care, various additional treatment options have been suggested by numerous small studies and reviews.[91,92] For most of these treatments however, results are variable and placebo controlled trials are difficult to accomplish because of the low incidence of

SJS and TEN and the large number of patients required for a study to be statistically meaningful. Unfortunately, all suggested therapies for SJS/TEN probably do not target the initiating events but rather abrogate later events once the process of epidermal apoptosis has started.

The only randomized controlled trial that has been conducted regarded thalidomide compared with placebo. This trial had to be ended because of an excess of deaths in, what later turned out to be, the active treatment arm. Thalidomide had been proposed because it is a potent inhibitor of TNF-α.[93]

Historically, corticosteroids were advocated, but after several reports with a negative outcome in the '80s, they were increasingly regarded as harmful and even detrimental by some authors.[2,94-98] The negative outcome was possibly due to the fact that low dose corticosteroids, given too long and too late in the process, are hardly therapeutically effective, raise the risk for infection, and possibly have a negative effect on wound healing. A short course of high dose corticosteroids, given early in the process however, might positively influence the immune mediated cascade, leading to apoptosis. This was the rationale to introduce an overall treatment protocol with high dosed pulse therapy with 1.5 mg/kg bodyweight dexamethasone on three consecutive days.[22,99] The general opinion on corticosteroids is less negative nowadays.[92] Based on retrospectively collected heterogeneous data from the EuroSCAR study, it was noted that, although corticosteroids did not have a significant effect on mortality in comparison with supportive care alone, a trend for a beneficial effect was seen.[100] Current opinion, according to most authors, is that systemic corticosteroids are clearly deleterious in the late stage of SJS/TEN, while in the early stage their benefit is not yet evidenced. The precise action of corticosteroids in inflammatory diseases is still not well understood. They have pleiomorphic immune modulating effects, e.g. through inhibition of numerous cytokines.[22,101]

The supposed rationale of intravenous immunoglobulins (IVIG) is their property for inhibiting activation by Fas-inhibiting antibodies of the death receptor; the reported clinical results however are not consistent and therefore controversial.[15,51,100,102,103]

Recently, a favourable outcome was mentioned for treatment with ciclosporin in an open trial (orally 3 mg/ kg/ day for 10 days, tapered over a month).[104] Other options such as plasmapheresis, aiming at clearing drug metabolites and cytokines, or cyclophosphamide, blocking immune activation, have also been suggested, all with varying results.[105-110]

Consultation of an ophtalmologist at an early stage of the disease can help to diminish the risk for permanent visual loss due to corneal scarring or neo-vascularisation. Failure to lyse adhesions and treat keratitis and corneal erosions can result in blindness. To rescue corneal epithelial cells, steroid pulse therapy and topical steroid application should be considered.[111,112] Sustained treatment using artificial tears and antibiotic and corticosteroid-containing ointments are warranted.[113,114] Amniotic membrane transplantation at the acute stage and scleral contact lenses have shown to be promising to prevent late sight-threatening cicatricial complications.[115,116] But even meticulous care can not always prevent long-term ophthalmologic sequelae.[32,117]

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1a. EEM with typical target lesions with round and well defined borders and three concentric zones.

1b. EEM with typical target lesions with round and well defined borders and three concentric zones.

1c. EEMM with typical target lesions with round and well defined borders and three concentric zones.

1d. Raised atypical targets.

2a. Flat atypical targets.

2b. SJS with erythematous macules, purpuric lesions and small erosions on the torso.

2c. SJS with haemorrhagic blistering of the lips.

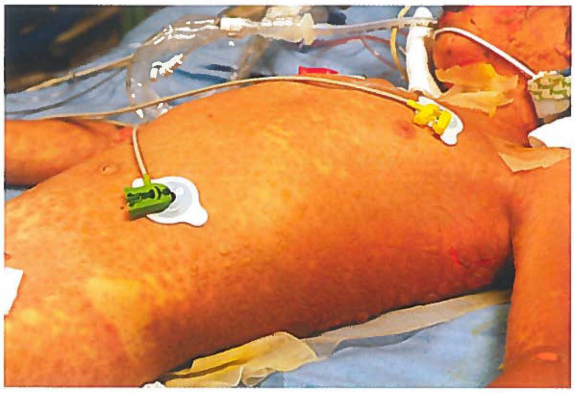
2d. SJS with erosive lesions on eyes, mouth, neck and upper thorax.

3a. SJS/TEN overlap with extensive blistering and erosions.

3b. SJS/TEN overlap with extensive blistering and erosions (late stage).

3c. SJS/TEN overlap with extensive blistering and erosions.

3d. SJS/TEN overlap with extensive blistering and erosions.



4a. Evolution of TEN, extensive erythema with spots and blistering.

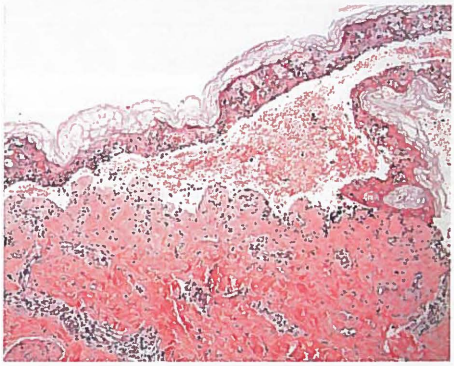
4b. Further evolution of TEN, extending erosions.

4c. TEN, healing phase with reepithelialisation.

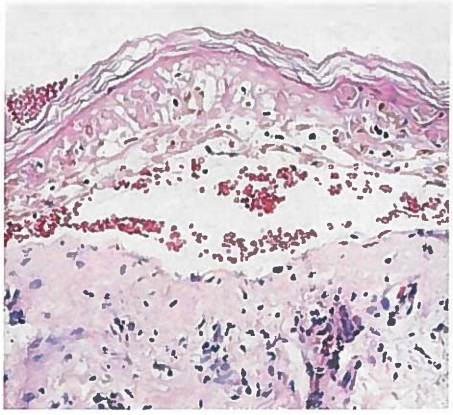
4d. TEN, healing skin with eye involvement.

5a. Hypo- and hyperpigmentation, 1 year after event.

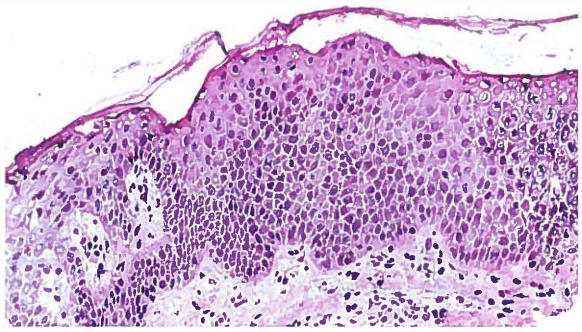
5b. Neovascularisation, 1 year after event.



6a. Early biopsy of TEN with evolving epidermal apoptosis and subepidermal blistering (H&E, original magnification 10 x10).



6b. Fully developed TEN with extensive epidermal necrosis (H&E, original magnification 20x10).



6c. SSSS with epidermal splitting at the stratum granulosum (H&E, original magnification 20x10).

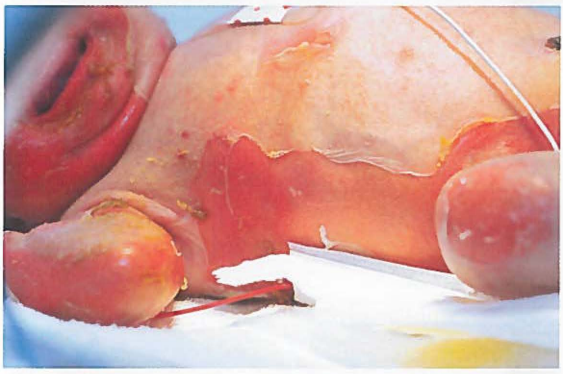
7a. EEMM with typical and atypical target lesions, evolving to blistering.

7b. Generalised bullous fixed drug eruption.

7c. Graft versus host disease.

7d. Second degree burn wound .

7e. Non-specific bullous drug reaction.



7f. Staphylococcal scalded skin syndrome.

7g. Paraneoplastic pemphigus.

7h. Paraneoplastic pemphigus.

7i. Subacute cutaneous lupus erythematosus.

7j. TEN-like systemic lupus erythematosus, early phase.

7k. TEN-like systemic lupus erythematosus, late phase.

1.3 Acute generalised exanthematous pustulosis (AGEP)

1.3.1 Introduction

Acute generalised exanthematous pustulosis (AGEP) is a rare, most often drug induced, severe pustular reaction pattern, characterised by an acute-onset and typical clinical picture and course.

In the past, most widespread sterile pustular eruptions were classified as generalised pustular psoriasis (GPP), a rare variant of psoriasis. In 1968, in a comprehensive review of 104 cases of GPP, Baker and Ryan identified on clinical grounds five cases of what they called "exanthematic pustular psoriasis".[1] These concerned non recurrent pustular eruptions with a very acute and short self-limiting course, presumably precipitated by infections and/or drugs, while a history of psoriasis was absent. In 1980, this reaction type was better characterized by Beylot *et al.* and termed "pustulose exanthématique aiguës généralisée" (PEAG).[2] Its translation, acute generalised exanthematous pustulosis (AGEP), is nowadays widely used for an uncommon clinical and histopathological pustular reaction pattern, demonstrating features discussed below. Subsequently, Roujeau *et al.* further described this reaction type in a larger series and observed psoriasis in quite a high number of patients in his series.[3] In 2001, the EuroSCAR study group proposed a standardised validation score system based on the morphology of the lesions, course of the disease, and laboratory and histopathological features (**Table 1**).[4] Nowadays, this validation score is generally used to establish the diagnosis of AGEP.

Pustular rashes similar to AGEP have been reported under various other names such as toxic pustuloderma, pustular drug rash, (subcorneal) pustular drug eruption or drug-induced GPP, and pustular psoriasiform eruption with leukocytosis.[5-10] Moreover, cases of AGEP have been classified as pustular psoriasis with or without recognising a drug as the etiologic agent, or interpreted as special variants of other pustular diseases.[11-13]

1.3.2 Epidemiology

The incidence of AGEP is estimated to be in the range of 1 to 5 cases per million per year in Western Europe; more representative data are missing.[4] Although AGEP can present at any age (mean 56 years), it is uncommon in children.[14,15] Primarily it was suggested that AGEP affects men and women equally; more recent reports however show a trend towards female predominance, with a men to women ratio of about 0.8.[4,15,16] Reported prevalence of a history of psoriasis is higher than could be expected from the general population.[3,15-20]

Table 1. Acute generalised exanthematous pustulosis validation score (EuroSCAR study Group)

Morphology		
Pustules	Typical	2
	Compatible	1
	Insufficient	0
Erythema	Typical	2
	Compatible	1
	Insufficient	0
Distribution/pattern	Typical	2
	Compatible	1
	Insufficient	0
Post-pustular desquamation	Yes	1
	No/insufficient	0
Course		
Mucosal involvement	Yes	-2
	No	0
Acute onset (≤ 10 days)	Yes	0
	No	-2
Resolution (≤ 15 days)	Yes	0
	No	-4
Fever ≥ 38°C	Yes	1
	No	0
Neutrophils : >7000/mm³	Yes	1
	No	0
Histology		
	Other disease	-10
	Not representative/no histology	0
	Exocytosis of neutrophils	1
	Compatible*	2
	Typical**	3

*Compatible: subcorneal and/or intra-epidermal non-spongiform or unspecified pustule(s) with papillary oedema or subcorneal and/or intra-epidermal spongiform or unspecified pustule(s) without papillary oedema. **Spongiform subcorneal and/or intra-epidermal pustule(s) with papillary oedema.
Interpretation: ≤ 0: no AGEP, 1–4: possible, 5–7: probable, 8–12: definite AGEP.

Sidoroff et al.[4]

1.3.3 Clinical characteristics

The clinical course of AGEP is very characteristic, showing an acute, quickly spreading eruption. In typical AGEP, dozens of small non-follicular sterile pustules arise on a burning and/or pruritic oedematous erythema (**Fig. 1a,b,c,d,e**). High fever above 38°C usually begins abruptly on the same day, or in a window of 2-3 days before or after onset of the pustular eruption. In most

cases, skin symptoms start in the face or in intertriginous areas (**Fig. 2a,b**) and extend to the trunk and lower limbs in a few hours, often with accentuation in the main folds (**Fig. 3a,b**). Although not typical for AGEP, additional skin symptoms can comprise marked oedema of the face and unspecific lesions such as purpura, 'atypical' targets or blisters.[3,4,21] Mild mucous membrane involvement on a single site (mostly oral) may occur in about 20% of cases.[3] After elimination of the culprit, pustules disappear in a few days, typically followed by post-pustular pin-point desquamation for a few days, while the reaction resolves within 15 days (**Fig. 4a,b**).[4] In 2005, the term acute localised exanthematous pustulosis (ALEP) was introduced to describe a localised pustular eruption on the face, otherwise fulfilling the criteria for AGEP.[22]

Cutaneous manifestations are often accompanied by systemic signs and symptoms such as fever, elevated neutrophilic blood counts (> 7 x 10^9/L in 90% of the cases), and mild eosinophilia (in 30%). Although internal organs are usually not evidently involved, renal function can be transiently slightly reduced (creatinine clearance < 60 mL/min in 30%), with features of "prerenal" kidney injury. Liver function tests are usually normal, but mild elevations of aminotransferase (< twice normal upper limit) and hypocalcaemia can be observed. No involvement of other internal organs has to be expected. The pustules are sterile, although secondary infection may occur.[1,3,4,23]

Overall prognosis is good, although lethal outcome has been reported. Complications and mortality (1-5%) are rare and are mostly seen in the elderly or patients in poor condition or with chronic diseases such as cardiovascular impairment. In those cases AGEP may precipitate death by an increased skin blood flow or super-infection of the lesions.[4,23,24]

1.3.4 Histopathology

Whereas the clinical picture and course of AGEP are usually very typical, the contribution of histopathology to diagnosis was less evident until recently, particularly for cases with a differential diagnosis of GPP. Previous knowledge on the histopathology of AGEP was mainly based on case reports and few small clinical studies, not providing a detailed description.[2,3,21,25-29]

Findings of a large multinational study in 2010, aimed at the description of the histopathological spectrum of AGEP were that the histopathology of AGEP is characterised by superficial spongiform pustules, spongiosis, exocytosis of neutrophils, necrotic keratinocytes, papillary oedema, mixed dermal infiltrates, including mid/deep-dermal and interstitial infiltrates, containing neutrophils and eosinophils, and the paucity of classical plaque-type psoriatic changes (i.e., Munro abscesses, absence of the granular layer, suprapapillary plate thinning, tortuous and dilated blood vessels) (**Fig. 5**).[20] A further single centre comparative study, aimed at a systematic histopathological description of both erythematous and pustular lesions in AGEP, and the acute and more chronic pustular lesions in GPP showed that differentiating features pointing at AGEP instead of acute GPP are the presence of eosinophils in the pustules or dermis, necrotic keratinocytes, mixed neutrophil-rich interstitial and (lower) middermal infiltrates, and

absence of tortuous, dilated blood vessels, while in addition epidermal psoriasiform changes are prominent in chronic GPP.[16]

1.3.5 Differential diagnosis

In view of the self-limiting character of AGEP it is essential to differentiate AGEP from a wide range of sterile, mainly non-follicular pustular eruptions. Most of these can easily be distinguished from AGEP on clinical and histopathological grounds, e.g. bacterial folliculitis, acne, dermatophyte infections, (bullous) impetigo, infantile chronic acropustulosis, Sweet syndrome, IgA pemphigus, necrolytic migratory erythema, bowel bypass syndrome, Behçet disease, impetigo herpetiformis, and staphylococcal scalded skin syndrome (SSSS). Differentiation from SJS/TEN, DRESS, subcorneal pustulosis (Sneddon-Wilkinsons disease), pustular vasculitis, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), and acneiform eruptions in targeted therapies can be more complicated.[30-33]

Presence of 'atypical' targets or blisters and extensive coalescence of pustules, resulting in a "positive Nikolsky's sign", detachment of the epidermis and superficial erosions, may give rise to some similarity with SJS/TEN (**Fig. 6a,b,c**) In such cases, histopathology is almost pivotal for differentiation, by showing subcorneal/intra-epidermal pustules in AGEP and full-thickness necrosis of the epidermis in TEN. The distinction is important because of the worse prognosis in cases with SJS/TEN.[33-35] Because DRESS may initially comprise papulovesicles or papulopustules it may resemble AGEP at first glance. However, pustules are less prominent and often follicular in DRESS, while also the prolonged course, different blood count abnormalities, and severity of visceral involvement allow distinction from AGEP.

Most challenging however is differentiation from pustulosis acuta generalisata, a post streptococcal disease arising mainly in children, and GPP, especially the acute von Zumbusch type.[16,36] Clinically, pustules in both AGEP and GPP are indistinguishable. Major differences however, are the more acute onset and short duration of symptoms in AGEP compared with GPP (mean duration fever and pustules 7.5 respectively 9.4 days versus 16.1 respectively 37.0 days) and recent drug introduction.[3] Moreover, additional lesions including petechial purpura, EEM-like atypical target lesions, vesicles or blisters on a background of a generalised pustular eruption may facilitate diagnosis of AGEP in cases where pustular psoriasis is also considered.[37] Occasionally, drug patch testing may help to narrow the differential diagnosis in ambiguous cases.[33]

1.3.6 Diagnostic Tests

Diagnosis is based on criteria, defined by the EuroSCAR study group (Table 1).[4] The value of in-vivo and/or in-vitro testing for the identification of causative drugs has been extensively demonstrated.[28,33,35,38] Both positive and negative patch tests and lymphocyte proliferation

responses to the culprit drugs have been observed in AGEP, although results are not always concordant.[28,35,39]

In-vivo patch testing is generally a safe and irrefutable method for determining the culprit drug. The proportion of positive drug patch tests in AGEP is approximately 50%, and up to 80% for certain antibiotics, which is higher than encountered in other types of cADR.[40-42] Moreover, patch-test reactions sometimes nicely mirror the events of the acute reaction and can be strongly positive.[33,35,43] Different in-vitro tests, including the lymphocyte transformation test (LTT), measuring lymphocyte proliferation and/or their cytokine release, macrophage migration inhibition factor test, interferon-gamma release test, and mast cell degranulation test may be of help in appointing the causative drugs, but are rarely performed in daily practice, due to their complexity, costs and efforts.[28,38,44-46]

1.3.7 Pathogenesis

Etiopathogenesis of AGEP is still not fully elucidated, although some progress has been made, particularly in the last decennium. The regularly observed tissue and blood eosinophilia, hallmark of many drug-induced allergic reactions, are in favour of a hypersensitivity reaction. This is also supported by positive patch test and/or LTT reactions towards the suspected culprit drug. Histology and immunochemistry of skin lesions, including those of positive patch test reactions, and immunochemistry of the LTT provide further clues for the pathogenesis of AGEP.[28,38,39,42] Drug-specific $CD4^+$ but also $CD8^+$ T cells can be isolated and cultured from patch test sites and blood of AGEP patients.[38,45,47-49]

AGEP appears to represent a peculiar subtype of delayed hypersensitivity type IV reaction where cytotoxic T cells emigrate and kill keratinocytes, with specific T cells playing a crucial role, producing large amounts of neutrophil-attracting cytokines, such as IL-8. This contributes to the accumulation of neutrophils in the skin lesions, an important characteristic of AGEP. Apparently T cells can be involved in some neutrophil-rich inflammatory responses, in which they may orchestrate the immune reaction directly by high IL-8/ CXCL8 production or indirectly via IL-22 production by Th 17 cells, inducing CXCL8 production in various cell types.[50] Drug-specific CXCL8-producing $CD4^+$ T cell clones revealed a predominant T helper cell (Th1)-type cytokine profile with high production of GM-CSF and IFN γ and various levels of the pro-inflammatory cytokine TNF-α.[48] The release of chemokines and neutrophil-activating cytokines (IL-4, IL-8, and GM-CSF), preferentially activates and recruits neutrophils, resulting in a type IVd immunologic reaction with blood neutrophilia and accumulation of neutrophils at the site of the lesions.[45,51] Moreover, it was recently appreciated that IL-8, apart from T cells, is also secreted by keratinocytes, enhancing neutrophilic inflammation and survival, attributing to sterile pustule formation.[45,52] Of note, neither IL-8 production nor neutrophilic infiltration is seen to such an extent in other types of drug allergy. Besides, few CXCL8+ T cells displaying a Th2-type cytokine profile with high IL-4 and IL-5 secretions may contribute to eosinophilia, regularly observed in AGEP.[45,48,52-54]

1.3.8 Risk factors

The etiological relation between drugs and AGEP is well described and more than 90% of all cases seems to be drug induced. Next to medicines, other causes such as acute viral infections (especially enterovirus such as Coxsackie virus A9 and B4, and echovirus 11 and 30, but also cytomegalovirus, Epstein-Barr virus, hepatitis B virus, and Parvovirus B19), Escherichia coli, Chlamydia pneumoniae, Mycoplasma pneumoniae, Echinococcus granulosus, spider bites, heavy metals (mercury), dietary supplements, chemotherapy, radiation and PUVA have been associated occasionally.[31] Of note, viral infections (e.g. Coxsackie B4/ Epstein-Barr virus) and vaccinations are relatively more often suggested as triggers in the paediatric population.[14,55,56] Analysis in a large case-control study however did not reveal a significant association with infections.[4,15]

Based on individual case reports and short series, dozens of medications have been implicated. Evaluation of risk factors for AGEP in the multinational case–control EuroSCAR study revealed a strong association with a broad spectrum of drugs, especially pristinamycin, ampicillin /amoxicillin, quinolones, (hydroxy)chloroquine, anti-infective sulphonamides, terbinafine and diltiazem.[15] Also carbamazepine and paracetamol are regularly mentioned as culprit drugs.[29,31] Interestingly, the EuroSCAR study revealed two different temporal patterns: after antibiotics a rapid onset of only a few hours to 2-3 days after drug introduction (median 1 day) was observed, while all other associated drugs had an interval of 1 to 3 weeks (median 11 days). This obvious peculiarity in the dynamics of the reaction may suggest different pathomechanisms. The short interval might indicate previous sensitization and/or an immunological recall phenomenon induced byT cell reactivation, directT cell activation, or activation of the innate immune system, whereas the longer latency time fits the classical pattern of primary sensitization. Another noteworthy finding in comparing studies of the EuroSCAR study group was the different spectrum of causative drugs in AGEP compared with SJS/TEN.[15,57,58]

Whether AGEP is an entity distinct from pustular psoriasis is sometimes raised as a point of discussion. Several studies show a higher prevalence of plaque-type psoriasis in AGEP than could be expected from the general population, suggesting that AGEP could be a reaction pattern favoured by a psoriatic background.[3,15,16,20,33] Patients with a pustular form of psoriasis and patients who develop a pustular drug reaction may share a common genetic background which directs them towards reacting with neutrophil-attracting mechanisms.[15] In a small study, human leukocyte antigen (HLA) B51 DRB1*07, DR11, and DQ3 were found more frequently in AGEP compared to the average population; further studies however are needed to confirm the hypothesis of genetic susceptibility to pustular drug eruptions linked to the major histocompatibility complex.[59] Of note, the *HLA-DRB1*07* allele is also associated with psoriasis.[60]

Mutations in genes that encode cytokines, their receptors or inhibitors, could also play a role. In GPP it was demonstrated that an aberrant interleukin by inhibiting an anti-inflammatory cytokine-induced response may lead to unregulated secretion of inflammatory cytokines (IL-8

in particular) by keratinocytes and pustular psoriasis.[61] Noteworthy, comparison of a sub-group of AGEP patients with a personal history of psoriasis showed no significant histopathological differences with cases without pre-existing psoriasis except for slight psoriasiform changes, especially the presence of tortuous/dilated blood vessels.[16] However, the fact that most drugs known to induce psoriasis, e.g. beta-blockers or angiotensin-converting enzyme (ACE) inhibitors, are not associated with AGEP, additionally supports that AGEP is different from psoriasis.[15]

1.3.9 Management and treatment

Early recognition of AGEP is of clinical relevance as discontinuation of the causative agent is the most important action to be taken. Due to its self-limiting course and favourable prognosis in most cases, specific treatment is generally not required. Corticosteroid treatment, often taken into consideration, is usually not necessary.[4,62] At present, no therapy has been evidenced to prevent extension of lesions or a further decline of patient's general condition. Sometimes supportive therapy is needed. Systemic antipyretics/ non steroidal anti-inflammatory drugs can be given symptomatically, provided they are not suspected to be the causative drug. Antibiotics should not be administered, unless there is super-infection of the skin lesions.

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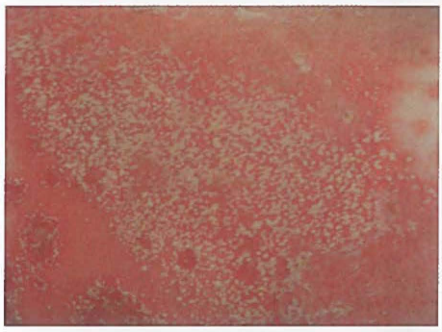
1a. Dozens of small non-follicular sterile pustules on oedematous erythema and atypical targets.



1b. Dozens of small non-follicular sterile pustules on bright erythema.

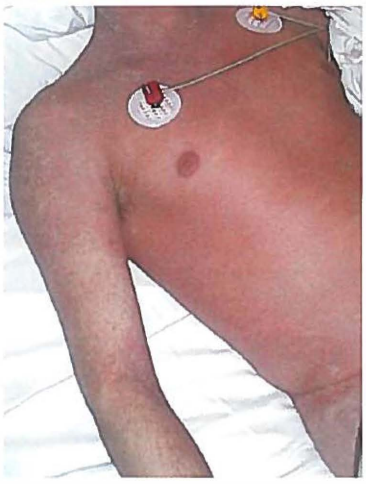
1c. Dozens of small non-follicular, partly confluent sterile pustels on oedematous erythema in pigmented skin.

1d. Dozens of tiny pin-headed non-follicular sterile pustules on oedematous erythema on the trunk.

1e. Detail 1a: lower arm and wrist showing dozens of pin-headed pustules.

2a. Early onset of the eruption on the axillary intertriginous area.

2b. Early onset of the eruption on the intertriginous area of the groin.

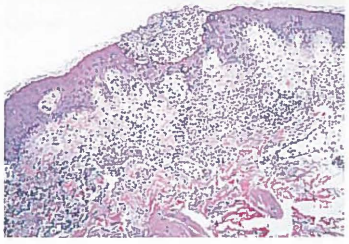


3a. Evolution with accentuation in the main folds: neck, axillary, ellbow, abdomen.

3b. Late stage, still with accentuation in the folds: axillary, submammary, ellbows, abdomen, groins.

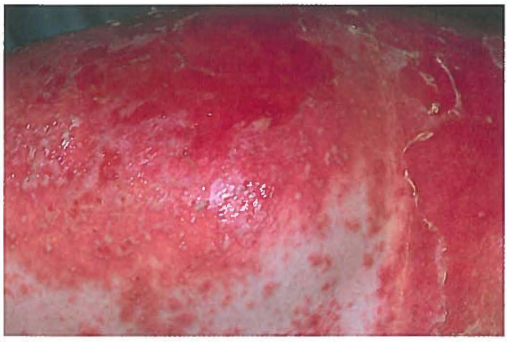
4a. Healing phase with post-pustular pin-point desquamation.

4b. Healing phase with extensive post-pustular pin-point desquamation.



5. Histopathology of AGEP. Slightly spongiform subcorneal-intraepidermal pustule, minor acanthotic rete ridge changes, spongiosis, neutrophilic exocytosis, papillary edema and mixed perivascular and interstitial infiltrates.

6a. TEN-like AGEP. Detail, showing pustules and superficial erosions.



6b. TEN-like AGEP. Detail, showing oedematous erythema, pustules and erosions.

6c. TEN-like AGEP, recovery phase.

1.4 Drug reaction with eosinophilia and systemic symptoms

1.4.1 Introduction

Reviewing the literature, a multitude of different names appears to describe a type of severe drug-induced hypersensitivity reaction with a distinct clinical reaction pattern.

In 1939, after their review on the toxic symptoms of phenytoin, Merritt and Putnam distinguished mild morbilliform eruptions, healing after withdrawal and most often not recurring after re-administration, from other eruptions with fever, exfoliative dermatitis and eosinophilia.[1] Later, lymphadenopathy and multivisceral involvement were associated as well. In 1950, after the association of systemic involvement, the reaction was recognized as a syndrome, often presenting with the classic triad of fever, rash, and lymphadenopathy.[2,3]

Since the early 1940s, shortly after introduction of hydantoin and its derivatives for convulsive disorders, drug reactions clinically and/or histopathologically mimicking malignant lymphomas were observed.[4] In 1959 Saltzstein grouped these observations from literature, added some new cases of lymphadenopathy induced by anticonvulsant drugs, and introduced the term drug-induced pseudolymphoma.[5] Thereafter, because the inciting drugs often were the same, both multisystem hypersensitivity reactions and drug-induced pseudolymphoma were sometimes interpreted as a single entity.[6-9]

Later however, it was recognized that both reaction types were two different kinds of adverse drug reactions (ADR): drug-induced pseudolymphoma having a more insidious beginning with nodules and infiltrated plaques appearing several weeks after the start of a drug without constitutional symptoms, histologically mimicking cutaneous lymphoma, and on the other hand an acute clinical entity associated with fever, a cutaneous eruption, lymphadenopathy, eosinophilia, and visceral involvement in which histopathology of the skin and/or lymph nodes may also mimic lymphoma.[8,10]

Since the landmark article of Merrit and Putnam, similar rare but potentially life-threatening ADR with cutaneous as well as internal organ involvement and eosinophilia have been repeatedly reported under a variety of names. The nosology often referred to the drug involved (e.g. dilantin/ dapsone/ sulfone/ allopurinol hypersensitivity syndrome), the most affected internal organ (e.g. nephritis, hepatitis), or the disease mimicked (e.g. mononucleosis-like illness, Kawasaki-like syndrome, pseudolymphoma).[3,8,11-18] After recognizing that several aromatic anti-epileptic drugs (AED) did cause similar symptoms, Shear and Spielberg coined the term anticonvulsant hypersensitivity syndrome in 1988 and suggested that this reaction due to AED was caused by a genetic defect in drug metabolism.[19] After hypothesizing that other drugs could elicit a similar reaction pattern, names and acronyms like hypersensitivity syndrome (HSS), drug reaction with eosinophilia and systemic symptoms (DRESS), drug induced delayed multi-organ

hypersensitivity syndrome (DIDMOHS) and drug (induced) hypersensitivity syndrome (D(I)HS) were proposed.[20-25]

Since the word hypersensitivity is rather uninformative and ambiguous, the more informative, clinically relevant acronym DRESS, was introduced by Bocquet *et al.* in 1996 to distinguish the syndrome from other cADR, not associated with systemic symptoms and eosinophilia.[22] This acronym is gaining use, although names, referring to e.g. the drug or most affected internal organ are still encountered. Also, full consensus on the definition of the entity and its precise criteria are still missing. Because a clinically meaningful name and a standardised definition are important for purposes of clinical recognition and further investigation, the RegiSCAR group proposed a score to validate potential cases of DRESS.[26]

1.4.2 Epidemiology

The incidence of DRESS is difficult to define due to the rarity of epidemiologic studies on the disease and inconsistencies in reporting, caused by a lack of consensus on nosology and case definition.[26-29] Moreover, because of the variability of the clinical and biological presentation, DRESS regularly goes unrecognized. However, the risk for developing DRESS by CBZ and phenytoine in new users within 60 days at first or second prescription was estimated at 1.0-4.1 in 10,000 and 2.3-4.5 in 10.000 respectively.[30] Although no sex or age predilection was observed in earlier reports, females were predominant and significantly younger than males in a recent large multinational study, especially for cases related to antiepileptics and antibiotics.[29,31]

1.4.3 Clinical characteristics

In its complete form, DRESS refers to a severe, idiosyncratic reaction, defined by a widespread and long-lasting skin eruption, accompanied by fever, lymphadenopathy, haematological abnormalities, and visceral involvement.[22,26,29,32] Because a single organ is usually dominant in its clinical presentation, DRESS may go unrecognised as a syndrome. Evolution of signs and symptoms is often relatively slow and can present in haphazard combinations, also in time, resulting in an academic approach from different medical specialties and treatment of individual symptoms.

Fever, often accompanied by malaise or pharyngitis, cervical lymphadenopathy and "rash" are often the first symptoms.[11,22,29,31-33] Mild to high-grade spiking fever, ranging from 38 to over 40°C, may persist for weeks and usually generates concern for an underlying infection; cultures however are negative.

The "rash" often starts with a morbilliform eruption, and is initially often hard to distinguish from benign drug eruptions or viral rashes. The face, upper trunk, and upper extremities are first affected; the eruption often extends and erythroderma or even exfoliative dermatitis may evolve.[22,31] Reported skin reactions however vary and include maculopapular (**Fig. 1a,b**), urticarial (**Fig. 1c,d**), erythematous, exfoliative (**Fig. 1e**), lichenoid (**Fig. 1f**), purpuric (**Fig. 1g**),

and eczematous-type reactions (**Fig. 1h**).[29,31,32] Blistering and sterile follicle-centred pustules may occur, as well as nonfollicular small pustules, while facial oedema is frequent (**Fig. 2a,b,c**).[11,22,29,31,34] Enlarged, tender lymph nodes, resolving slowly after cessation of the inciting drug, are frequent as well.[29,31]

Haematologic abnormalities are quite characteristic and concern leukocytosis, often with prominent eosinophilia, and mononucleosis-like atypical lymphocytes.[10,29,31,32] Hyperleukocytosis can be considerable, sometimes above 50×10^9/L.[22,29] Also neutrophilia in the initial phase and monocytosis later in the reaction are frequently met.[29] An absolute eosinophil count of more than 1.5×10^9/L, which is regularly encountered in DRESS, is toxic to endothelial cells and can lead to cardiac, gastrointestinal, central nervous system, pulmonary, and renal dysfunction, including coronary artery thrombosis and eosinophilic pneumonia.[35,36] Although haematological abnormalities can point towards a diagnosis of DRESS, viral infections such Epstein-Barr virus infections or haematologic diseases can be difficult to distinguish.

Most common participating viscera are the liver, kidney, and lungs.[29] Isolated elevation of liver transaminases is usual, but (acute) liver failure due to massive hepatocellular necrosis may occur and accounts for the principal cause of mortality.[3,12,29,32,37,38] Hepatitis, generally anicteric but sometimes presenting as hepato-splenomegaly, may worsen during several weeks after drug withdrawal and may take months to resolve completely.[11,31,32] Other organ involvement includes (interstitial) nephritis/ pneumonitis, heart failure (eosinophilic myocarditis), pericarditis, symptoms of the central nervous system (meningo- encephalitis), tonsillary pharyngitis, arthritis, myalgia, myositis and sporadically hypothyreoiditis, diabetes and pancreatitis.[11,15,16,22,29,31,32,39-41] Shock with respiratory distress and hypotension has also been also described. Sequential reactivation of several herpes viruses, especially human herpes virus type 6 (HHV-6), can be observed and is often regarded responsible for a more severe or protracted course.[42,43]

The onset of DRESS is more delayed than most other cADR, often starting 2-6 weeks after initiation of the inciting drug, although latency time can be shorter when the drug was supplied previously. Due to clinical similarity to e.g. infectious diseases, the relatively long latency, and the prolonged course, even after withdrawal of the culprit drug, diagnosis of DRESS may be delayed or the reaction goes unrecognized as drug-related.

1.4.4 Prognosis/sequelae

DRESS is serious and may cause considerable morbidity and mortality. The mortality rate, mostly due to visceral involvement, is estimated at near 10%, but is not exactly known since the incidence of the reaction is unknown due to misdiagnosis and underreporting.[40,44] In particular liver and renal involvement can be serious, even necessitating transplantation and/or dialysis.[45] Otherwise, recovery is usual and total after drug withdrawal, although particularly the skin eruption and hepatitis may persist for weeks and sometimes even months. Rechallenge with

the offending drug results in a quick recurrence of signs and symptoms. Even near-fatal liver necrosis has been reported after re-administrating small amounts of phenytoin.[46]

1.4.5 Histopathology

Histopathology of the skin can vary substantially, in parallel with the variability in clinical appearance. Rather dense diffuse or superficial and perivascular lymphocytic infiltrates with variable amounts of eosinophils and dermal oedema are seen regularly. Intraepidermal vesiculo-pustules may occur; focal vacuolar degeneration of the basal layer, band-like infiltrates, sometimes including atypical lymphocytes, and epidermotropia mimicking lymphoma can be observed (**Fig. 3a,b,c,d**).[8,22,31,47,48]

1.4.6 Differential Diagnoses

Because of the variability of signs and symptoms DRESS may resemble several other diseases and it is typically a diagnosis by exclusion.[26,29,44] Differential diagnostically one might consider in particular other cADR including AGEP and SJS/TEN, acute infections including bacterial sepsis, SSSS, toxic shock syndrome, acute viral infections (including Epstein-Barr virus, hepatitis virus, influenza virus, cytomegalovirus, human immunodeficiency virus), Kawasaki syndrome, Still's disease, (pseudo)lymphoma, idiopathic hypereosinophilic syndrome, collagen diseases, and angioimmunoblastic lymphadenopathy.[4,5,8,18,44,49-51]

In some cases of SJS/TEN with systemic involvement, most often of liver or lungs, overlap with DRESS may be suggested, however visceral involvement in SJS/TEN is generally milder than in DRESS.[52] Also, cases with DRESS with blistering might suggest such overlap, but blisters in DRESS are more limited, caused by dermal oedema, and tense instead of flaccid as in SJS/TEN. Moreover, mucosal involvement in DRESS is not prominent, generally mild and not haemorrhagic. Most important for differentiation is a strict application of the case definition of both conditions.[26,53] Because DRESS may initially comprise papulovesicles or papulopustules it might resemble AGEP. However, pustules in DRESS are less prominent and often follicular, while a prolonged course, differences in blood count abnormalities, and severity of visceral involvement also allows differentiation from AGEP.

1.4.7 Diagnostic Tests

Rechallenge, including re-administration of a small test dose of the suspected culprit, should not be performed in DRESS as it may result in a quick recurrence of signs and symptoms and even near-fatal reactions.[46] Other in vivo and also vitro testing with the suspected drug(s) may be helpful to confirm diagnosis and assign the culprit. Sensitivity and specificity of these tests however, are variable, depending amongst others on the drug involved, and testing should only be performed when the reaction has subsided.[54,55]

Santiago *et al.* observed positive patch test reactions in 32.1% of DRESS cases, most often elicited by AED, in particular CBZ.[55] The sensitivity of the lymphocyte transformation test (LTT) in DRESS has not yet been established in larger series; some authors however, report frequent positive test results.[56,57] More sensitive in vitro lymphocyte reactivity in peripheral blood mononuclear cells might be yielded by flow cytometry, the ELISA test, or a combination of both, by measuring inflammatory cytokines, especially IL-5, instead of proliferated lymphocytes.[56,58,59] Test results however, can be markedly influenced by their timing. Actually, in several cases a positive LTT was not obtained until 3 months after the onset of the disease.[57,60]

The in vitro lymphocyte toxicity assay with the suspected drug(s) could provide an additional diagnostic tool in increasing the accuracy of causality assessment of the likely agent. Additionally, this method could serve as a screening test for potential 'cross-reacting' drugs by measuring the lymphocyte phenotypic detoxification systems.[19,61]

1.4.8 Pathogenesis

DRESS represents an idiosyncratic delayed immunologic reaction, probably to rather a limited number of drugs. Pathogenesis appears to be multifactorial, involving immunological mechanisms and particular drug detoxification pathways. Although several theories have been proposed, complete pathogenesis is still unknown. The long latency time after start of medication suggests involvement of idiosyncratic metabolic mechanisms, and also supports a role for viral infections in triggering and/or activation of DRESS. DRESS is possibly the result of a cascade of successive events on a predisposed genetic background.

It has been demonstrated that reactive metabolites rather than their parent drug can be responsible for idiosyncratic drug reactions.[32] Pharmacogenetic variations in drug metabolism and detoxification are important and slow acetylation is probably one of the risk factors; a slow acetylator phenotype and increased susceptibility of lymphocytes to toxic hydroxylamine metabolites in vitro have been associated with an increased risk of developing DRESS to sulfonamides.[22,62-64] A relation between DRESS due to AED or sulfonamides and an individual genetic defect of the enzymes involved in the metabolic cascade of these drugs has been suggested since long, implying siblings may be at increased risk of developing the same reaction.[62,65]

After bio-transformation of e.g. aromatic AED by cytochrome P-450, insufficient detoxification can result in accumulation of reactive toxic metabolites (arene oxide intermediates). These metabolites can bind to tissue macro-molecules and may cause cell damage or cell death, or act as a hapten and provoke an immune response. Insufficient detoxification has been suggested to be based on a genetic defect for the enzyme epoxide hydroxylase. This "toxic metabolite theory" can be substantiated by a lymphocyte toxicity assay.[32,63,65-67]

Besides, a relation between viral infections and the simultaneous or subsequent development of allergic inflammation has been observed in various clinical situations. Examples of a role

for virus are the strongly increased risk in HIV-positives to develop severe drug reactions, in particular for sulfamethoxazole, and the increased risk in EBV infection for ampicillin rashes. It is further hypothesised that viral infections may induceautoantibodies against cytochrome P-450 enzymes and that reactivation of HHV-6 may have potentially serious interactions with enzymes that detoxify drugs, such as cytochrome P-450.[48,68] More recent studies suggest an intimate relationship between reactivations of herpes viruses, especially HHV-6, and the development of DRESS. Reactivation of herpes viruses is even considered a criterion by Japanese experts, and often held responsible for a more severe and/or protracted course.[25,43,48,69-75]

A transient state of immune suppression with subsequent reactivation of latent virus infections has been observed in DRESS. In DRESS two phases can be distinguished: the initial immunosuppressive phase accompanied by the ADR, and the second, the viral reactivation phase with exacerbation of the clinical symptoms. Immunomodulating effects of specific drugs such as anticonvulsants, minocycline, allopurinol and sulfonamides, presumably also promote HHV-6 reactivation.[76,77] Moreover, sequential reactivation of several herpes viruses is sometimes observed, a phenomenon that can also be seen in immunocompromised patients with graft-versus-host disease.[42,72,73,78]

Contrary to TEN, which shows transitory impairment in the function of regulatory T cells (Tregs), DRESS displays a dramatic expansion of functional Tregs during the acute phase. Hypogammaglobulinemia and a profound decrease in the number of B cells can be found at the onset of DRESS, probably related to the expansion of functional Tregs, that possibly induce B cell-death. The vast population of Tregs may also prevent activation and expansion of antiviral T cells, thereby reducing lesion severity and possibly allowing latent herpes viruses to reactivate in an uncontrolled way.[79] Antiviral cytotoxic T cells probably play the most important role in controlling viral reactivation; virus-specific $CD8^+$ T cells for instance can prevent herpes simplex virus reactivation.[80] After resolution of DRESS a gradual loss of the function of Tregs may increase the risk of subsequently developing autoimmune diseases.[79]

1.4.9 Risk factors

By definition, DRESS is drug-induced. For the first time, this type of reaction was described for phenobarbital and phenytoine, and later also for the other older AED such as CBZ, and primidone.[2,3] Cross-sensitivity between these older AED is very frequent (70-80%).[19,22] Later, DRESS was also associated with sulphonamides such as sulfasalazine and dapsone, and allopurinol, minocyclin, mexiletine, lamotrigine and few other drugs.[8,20,22,29,43,48,81-85] Compared to other SCAR, the number of drugs implicated seems far more limited, with AED, especially CBZ, allopurinol and sulphonamides in the leading position, while latency time after drug introduction is usually longer.[29]

Since long it has been suspected that DRESS may have a genetic background, suggesting a direct involvement of HLA in the pathogenesis of drug hypersensitivity when the HLA molecule

presents the binding site for an antigenic drug inducing T cell activation. Recently it was found that the HLA-B*5801 allele presents an important genetic risk factor for allopurinol-induced DRESS and SJS/TEN, especially in the Han Chinese, whereas only a moderate association was observed in the European and Japanese population with this allele, so apparently ethnicity also matters.[86-89] Moreover, the HLA-B*5801 allele is far more prevalent in the Han Chinese. However, since up to now only for few drugs a strong genetic association is found, more research is needed to clarify yet unknown risk factors and to explore further the pathophysiology of these reactions, so that better diagnostic tests and treatment methods can be developed. The high sensitivity and specificity of some markers provide a plausible basis for developing screening tests to identify individuals at risk for this type of drug hypersensitivity. Taking into account the rarity of the disease, further refinement of the pharmacogenetic base depends on future international collaborative efforts.

1.4.10 Management and Therapy

Early recognition, followed by prompt withdrawal of the culprit drug is the most decisive step to avoid disease progression, unnecessary investigations and treatment, thus potentially resulting in less morbidity and mortality and restoring health.

The benefit of an accelerated elimination of the causative drug and other specific therapeutic interventions remains to be established since only few studies have focused hereon and controlled studies regarding management of DRESS are lacking. Management is aimed at (muco)cutaneous as well as systemic care, including close observation and supportive care with strict attention to hydration and electrolyte balance, prevention of infection, and, if still needed, alternative treatment of the original disease, e.g. epilepsy. Cutaneous symptoms respond well to antihistamines and high-potency topical steroids.[31] Severe erythroderma or exfoliative dermatitis significantly increases the cutaneous blood flow, raising risk for cardiac failure, particularly in the elderly or those with prior cardiac impairment. Oral antipyretics and topical corticosteroids are helpful to decrease this risk, while for exfoliative dermatitis local antiseptics can be added.[44]

Systemic corticosteroids can reduce symptoms of delayed hypersensitivity reactions; they are known to inhibit for instance the effect of IL-5 on eosinophil accumulation in vivo.[90] Accumulation of eosinophils is believed to attribute to internal organ involvement in DRESS. As in other allergic diseases, preactivation or priming of eosinophils by (proinflammatory) cytokines is important in DRESS. Several priming-dependent eosinophil responses, such as migration and adhesion, are reduced by treatment with corticosteroids.[91] Although the role of corticosteroids is still not evidenced in DRESS, systemic corticosteroids are often administered in cases with internal organ involvement.[11,22,92] Most clinicians start prednisone at a dose of 0,5–2 mg/kg per day when signs or symptoms are severe.[32] Dramatic improvement in clinical symptoms and laboratory abnormalities is usually observed soon after corticosteroid therapy,

but its impact on the long term disease course is not known, and internal manifestations seem not always to be reversed.[31,34,92] Noteworthy, relapses can be observed when corticosteroids are tapered and withdrawal of steroid treatment may result in a rapid return of the symptoms followed by resolution at readministration.[22,92,93] HHV6 (re)activation, potentially promoted by systemic steroids could be responsible for these relapses. While waiting for better evidence, it is probably wise to recommend systemic steroids only for patients with life-threatening visceral manifestations such as interstitial pneumonitis or nephritis. Administration of other immunosuppressive agents (e.g. cyclophosphamide, cyclosporine) has also been suggested, mainly for patients that are not improving after discontinuation of the offending agent and high dose corticosteroid administration.[94] To address the state of transient immunosuppression, IVIG could have a rationale.[95,96] Other treatment options mentioned are interferon and N-acetylcysteine.[97]

To prevent recurrences, it is essential to avoid the suspected drug, including cross-reacting drugs. Cross-reactions are especially frequent between the older AED, making it difficult to find a safe alternative. Because of a potential genetic predisposition, first-degree relatives should be informed on a potentially elevated risk for DRESS when using the same or cross reacting drugs.[98]

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1a. DRESS with maculopapular eruption on trunk and arms.

1b. Detail 1a. with firm erythematous papules on the belly.

1c. DRESS with urticarial exanthema on trunk and arms.

1d. Detail of urticarial exanthema on arm.

1e. DRESS with exfoliative presentation on the trunk.

1f. Lichenoid presentation on the trunk with detail.

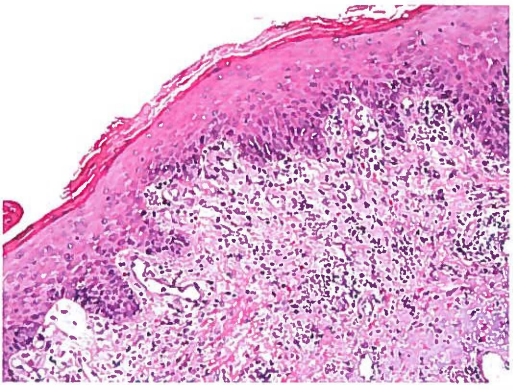
1g. DRESS with purpuric presentation.

1h. DRESS with an eczematous presentation.

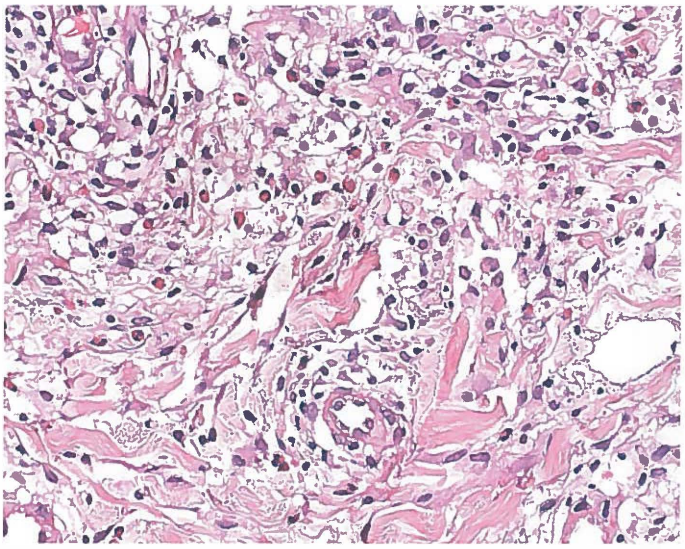
2a. Peri-orbital oedema, scaling, and residual facial erythema.

2b. Peri-orbital oedema, scaling, and residual facial erythema.

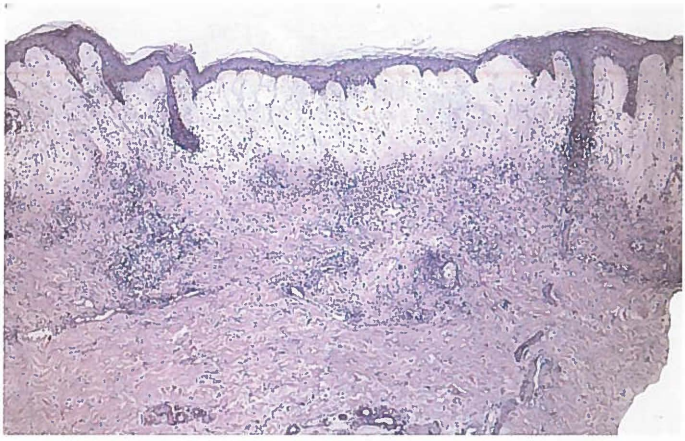
2c. Facial oedema, scaling, and residual facial erythema and pustules.



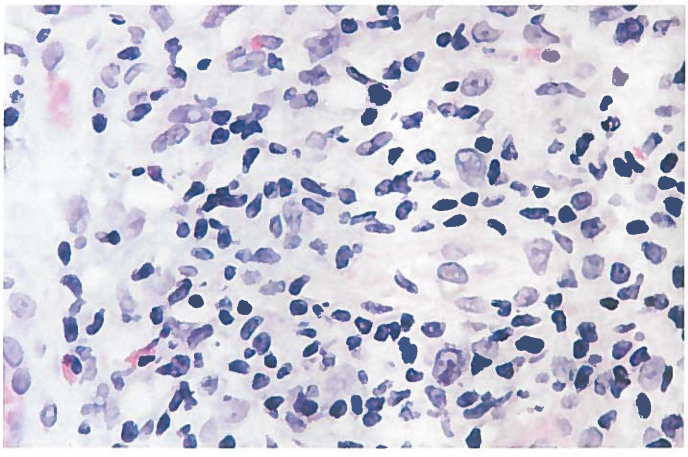
3a. Hyperkeratosis with parakeratosis, diffuse superficial perivascular and interstitial infiltrates with variable amounts of eosinophils (H&E, original magnification 10x10).



3b. Detail 3a of dermal infiltrate showing several eosinophils (H&E, original magnification 40x10).



3c. Extensive superficial dermal oedema and dermal, mainly perivascular, mixed infiltrates (H&E, original magnification 5x10).



3d. Detail of dense band-like dermal infiltrate containing lymphoid cells including large cerebriform mononuclear cells (some in mitosis), many histiocytes, and eosinophils H&E, original magnification 40x10).

1.5 Aims and outline of this thesis

This thesis addresses challenges in case definition, diagnosis and treatment of a number of SCAR: SJS/TEN, AGEP, and DRESS.

Chapter 2 describes the results of treatment with dexamethasone pulse therapy in a series of patients with SJS/TEN. Although treatment of SJS/TEN with corticosteroids became highly controversial in literature since the mid 80's of the past century, corticosteroids are worldwide still regularly administered.
Chapter 3 focuses on detection of differential diagnostic clues in bullous manifestations in SJS/TEN and (S)LE, and evaluation of the prevalence of (S)LE in a large population based cohort of SJS/TEN patients.

Chapters 4 and **5** are complementary to each other. **Chapter 4** describes the spectrum of histopathological features in a large, multinational, validated series of patients with AGEP, while **chapter 5** is aimed at differentiation of AGEP and GPP, based on histopathological features, in a single centre series.
Chapters 6a and **6b** are also complementary to each other. Both chapters describe a case of AGEP caused by morphine, a drug rarely implicated in cADR and not earlier reported as causative agent for AGEP. Moreover, the use of in-vitro and/or in-vivo testing in AGEP is addressed in both cases. Of note, the patient in chapter **6b** showed features, resembling TEN.
Chapters 7 and **8** describe two cases of less serious cADR which due to the presence of pustules next to bright erythema had AGEP in their differential diagnosis. These cases, in **chapter7** with a type B reaction and in **chapter 8** with a type A reaction, demonstrate that also other conditions than SCAR may mimic AGEP.

Chapters 9 and **10** are complementary, and address the issue of the case definition of DRESS. This hypersensitivity reaction is a topic in dermatologic literature for over 50 years, under a multitude of names and case definitions. In **chapter 9** a diagnostic validation score is presented, while in **chapter 10** the features, validated according to this score in a first large multinational series, are presented. The proposal for consensus on unification of case definition and criteria has met a positive response in literature since its publication.

In **chapter 11** the interesting observation is presented that "homing" of drug specific T cells in the skin probably also plays a role in cADR. The observation also underlines that clinically negative patch tests are no absolute proof of absence of a hypersensitivity reaction.

2

Dexamethasone pulse therapy for Stevens-Johnson syndrome/toxic epidermal necrolysis.

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Summary

Mortality in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) is high. Apart from intensive supportive therapy, no generally accepted specific treatment regimen exists. The role of corticosteroids in SJS/TEN is controversial. It is possible that high-dose pulse therapy with corticosteroids might be an improvement compared to long-term lower dose therapy, by combining higher efficacy with a diminished risk both of infection and of delayed wound healing. The aim of this study was to evaluate the efficacy of dexamethasone pulse therapy with respect to mortality and healing time of patients with SJS/TEN. A small, uncontrolled series of consecutive inpatients with SJS/TEN was treated with dexamethasone pulse therapy. The efficacy of this treatment was assessed retrospectively using SCORTEN. Twelve patients were included over a period of 10 years. One patient died, while SCORTEN predicted a fatal outcome of 4 patients. Stabilization was reached after 2.3 days on average, total re-epithelialization after 13.9 days. The results of this study bear no statistical relevance due to the small number of patients. In conclusion, short-term dexamethasone pulse therapy, given at an early stage of the disease, may contribute to a reduced mortality rate in SJS/TEN without increasing healing time. A larger controlled trial is warranted to investigate further the use of dexamethasone pulse therapy in SJS/TEN.

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but serious mucocutaneous reactions with extensive epithelial sloughing and systemic symptoms, most often caused by drugs.[1] More than 100 drugs have been associated with SJS/TEN, most often implicated are anti-epileptics, sulphonamides, β-lactam antibiotics, non-steroidal anti-inflammatory drugs and allopurinol. SJS and TEN are part of a spectrum, which is artificially divided into 3 groups: SJS when the total detached and detachable body surface area (TBSA) is less then 10%, TEN when it is over 30%, and SJS/TEN-overlap when it is between 10% and 30%.[2] The incidence of SJS is 1.2–6 per million per year and that of TEN 0.4–1.2 per million per year.[1] Mortality rates reported in the literature vary due to differences in the definition of SJS and TEN, in populations and in treatment, but they are generally high. In adults mortality due to TEN is most often cited as 30–50%.[1,3-5] Sepsis and multi-organ failure are the main causes of death. Recovery is usually slow and may take 3–6 weeks.[1] As a rule skin lesions heal without scarring, whereas mucosal scarring and strictures are frequent late complications. Late eye complications, potentially leading to blindness, occur in up to 50% of cases.[6]

Apart from intensive supportive therapy, a generally accepted regimen for specific treatment of SJS/TEN is lacking. Treatment options include systemic corticosteroids, intravenous immunoglobulin therapy (IVIG), other immunosuppressive therapy, or no systemic treatment. Historically high-dose corticosteroids were advocated, but since the mid-1980s the use of corticosteroids in SJS/TEN has been controversial and is even considered detrimental by some authors.[1,7-9]

Intravenous (i.v.) pulse therapy with corticosteroids is used in severe, often autoimmune, diseases, as it is assumed to share high efficacy with fewer side-effects than long-term lower dose corticosteroids. It has been used in dermatology since 1982 for several dermatological diseases that are often refractory to standard therapy, such as pyoderma gangrenosum and pemphigus.[10] Although we demonstrated recently that there was no benefit of giving long-term adjuvant oral corticosteroid pulse therapy in addition to conventional treatment in patients with pemphigus vulgaris, the hypothesis that i.v. corticosteroid pulse therapy could be useful in TEN is still valid, since the pathomechanism of both diseases is different, and corticosteroid pulse therapy is applied as short-term monotreatment in TEN.[11] There are only a few case reports describing pulse therapy in TEN.[12,13] Initially, 1000 mg methylprednisolone was usually used, but recently dexamethasone has often been chosen for pulse therapy because it combines a strong immunosuppressive glucocorticoid with a negligible mineralocorticoid effect. We studied the effect of dexamethasone pulse therapy (DPT) in 12 patients with SJS/TEN.

Methods

From 1993 to 2003, we treated 12 consecutive patients who were referred to our department with SJS/TEN, using a standardized care protocol that did not require ethics review from our institution. All data were analysed retrospectively.

After anamnesis and physical examination, diagnosis was verified by histopathology of direct fresh-frozen sections of the skin, enabling quick diagnosis and differentiation from other diseases, especially staphylococcal scalded skin syndrome. Diagnosis was subsequently confirmed by routine histopathology, while immunofluorescence analysis of the skin and serum was performed in order to exclude immuno-bullous diseases. The date of onset of disease was determined from the patient's medical history. Assessment of drug culpability (i.e. the empirical risk of a drug and the time-relation between drug use and the adverse reaction) was also based on the patient's history. All suspected and non-essential drugs were stopped. Demographic and specific disease data are presented in **Table 1**.

Table 1. Clinical characteristics of patients with toxic epidermal necrolyis (TEN) o r Stevens-Johnson syndrome (SJS)

Pat. no.	Age (years)/ Sex	TBSA on admission	TBSA max.	No. of mucosal sites involved	Diagnosis	SCORTEN on admission
1	71/M	26	32	5	TEN	4
2	33/M	45	62	4	TEN	2
3	44/F	30	72	5	TEN	2
4	15/M	3	9	3	SJS	0
5	62/F	60	70	3	TEN	3[a]
6	70/F	18	19	3	SJS/TEN	3
7	78/M	23	41	2	TEN	5[a]
8	53/F	53	61	4	TEN	3
9	58/F	11	20	2	SJS/TEN	3[b]
10	77/M	6	19	2	SJS/TEN	3
11	84/F	20	29	2	SJS/TEN	3
12	22/M	25	48	2	TEN	2[c]
Mean	55.6	26.7	40.2	3.1		2.8

[a] Brain tumour/metastasis.

[b] Systemic lupus erythematosus (SLE).

[c] Bone marrow transplant for haematological malignancy.

TBSA, total detached and detachable body surface area in %.

Specific systemic therapy was started as soon as the diagnosis was established. In the first 4 patients we combined i.v. dexamethasone 100 mg, given within 30–60 min on 3 consecutive days, with one dose of cyclophosphamide 500 mg on the first day, analogous to the pulse for

pemphigus vulgaris used by Pasricha.[14] After the fourth patient, cyclophosphamide was omitted and the regimen changed to i.v. dexamethasone 1.5 mg/kg body-weight as pulse therapy for 3 consecutive days.

The patients were seen by a multidisciplinary team and received intensive supportive care according to a standard protocol. This included early fluid and electrolyte replacement, aggressive nutritional supplementation, and monitoring of vital functions. An ophthalmologist was routinely consulted about daily eye care. Meticulous wound care included lubricants, topical antibiotics and non-adhesive silicone wound dressings. Nursing was barrier protected and the patients were treated on an air-fluidized bed in a specialized humidity- and temperature-controlled unit with, for aseptic reasons, a laminar down-flow stream. Epidermal involvement and TBSA were charted daily to determine the date of arrest of progression and of complete re-epithelialization (**Table 2**). Additional investigations, including haemograms, biochemical tests, urine analysis, coagulation tests, fluid balance, body weight and bacteriological analysis, were performed on a regular basis. The use of lines and catheters was avoided as much as possible,

Table 2. Suspected drugs and course of the disease (in days) before and after dexamethasone pulse therapy (DPT)

Patient no.	Suspected drug	Lag time[a]	Blister to DPT	DPT to stabilization	DPT to healing	Blister to healing	Remarks
1[b]	Sulphamethoxazole + trimethoprim	2[c]	1	2	72	73	Burn scars, HSV
2[b]	Acetylsalicylic acid	<14	3	2	15	18	
3[b]	Carbamazepine	12	1	2	17	18	
4[b]	Carbamazepine	14	2	2	8	10	
5	Phenytoin	36[d]	6	2	24	30	Late referral, HSV
6	Allopurinol	5	4	1	14	18	
7	Phenytoin	37[d]	1	3	9	10	
8	Carbamazepine	17	2	2	17	19	
9	Omeprazole	29[d]	4	3	14	18	
10	Amoxicillin + clavulanic acid	4	3	5	14	17	
11	Terbinafine	19	2	1	12	14	
12	Sulphamethoxazole + trimethoprim	10	4	3	9	13	
Mean 1–12			2.8	2.3	18.8	21.5	Overall
Mean 2–12			2.9	2.4	13.9	16.8	Excluding case 1

[a] Lag time: time between first drug administration and first blister.

[b] Also received cyclophosphamide 500 mg on day 1.

[c] Eight years earlier: toxic epidermal necrolysis after sulphamethoxazole + trimethoprim.

[d] Chronic corticosteroid use: daily dose equivalent to 15–30 mg prednisolone.

HSV: herpes simplex virus.

and the venous line was maintained as short as possible. H2-blocking agents were administered in case of a history of gastric upset. To prevent intestinal Candida overgrowth we supplied oral nystatin, and for thrombosis prophylaxis nadroparin was given subcutaneously. Pain killers and sedatives were provided as needed. Antibiotic prophylaxis was not given, but antibiotics were supplied immediately when clinically warranted. After discharge, a follow-up of 8±2 weeks was performed, and in cases where late sequelae were observed, also 2 years later.

SCORTEN, a validated TEN-specific severity-of-illness-score, ranking severity and predicting mortality, was calculated retrospectively to assess the efficacy of DPT. SCORTEN is based on seven independent risk factors (age, heart rate, malignancy, TBSA, and serum urea, bicarbonate and glucose levels). The predicted mortality progressively depends on the number of factors present.[15]

Results

Twelve consecutive patients (6 males, 6 females) were treated. Their mean age was 55.6 years (age range 15–84 years). TBSA and characteristic cutaneous findings led to the classification of 1 SJS, 4 SJS/TEN-overlap and 7 TEN. In all patients, 2 or more mucosae were affected. The mean SCORTEN on admission was 2.8 (range 0–5) and predicted a mortality of 4 cases (25%). The mean delay between occurrence of first blister and first DPT was 2.8 days (range 1–6 days). Disease stabilization was achieved after a mean of 2.3 days (range 1–5 days) after DPT. The mean time of healing (not stabilization) was strongly influenced by patient 1, who had extensive pre-existing burn scars. When we exclude these data, healing time from first DPT was 13.9 days (range 8–24 days), while from first blister it was 16.8 days (range 10–30 days).

Patient 7 died; according to the consulting neurologist the cause of death was brain oedema due to metastasis, while his skin had practically healed. All other patients survived without major sequelae. Sepsis was found in patients 1 and 2, and suspected in patient 5. In addition, patients 1 and 5 had serologically proven herpes simplex virus (HSV) type 1 infection while leukopaenia was present, probably contributing to protracted healing. In patient 1 neutropaenia (0.04×10^3/µl) accompanied severe leukopaenia (0.4×10^3/µl). In patients 2 and 3 the respiratory tract was involved, leading to respiratory insufficiency; patient 3 needed mechanical ventilation. Though all patients experienced eye involvement in the acute phase, late sequelae were relatively mild and severe impaired vision was not encountered. Patients 2 and 8 developed mild trichiasis, while patients 2 and 12 were left with dry eyes. Five patients (nos 2, 3, 4, 8 and 12) experienced hyper- and/or hypo-pigmentation of the skin, most often transient. Hypohidrosis and dystrophic nails were observed in patient 8. Apart from slight transient glycaemia in some patients that might have been caused by dexamethasone, we did not observe any side-effects of dexamethasone.

Discussion

The pathophysiology of SJS/TEN is not yet fully elucidated, although significant progress has been made. Massive accelerated apoptosis has been proposed as the main mechanism underlying keratinocytic death in SJS/TEN. Several pathways can lead to apoptosis. CD8-positive T cells and macrophages play an important role in the extensive epithelial necrosis and subepithelial detachment.[16] Various (pro)inflammatory cytokines including tumour necrosis factor (TNF)-α may contribute to epidermal cell death, as well as to fever and malaise. It has been suggested that, in SJS/TEN, apoptosis is mediated principally through activation of the Fas receptor by increased Fas ligand expression, but others have suggested that it is mediated mainly by TNF-α, perforin and granzyme B. Interferon-γ up-regulation of keratinocytes also plays a role.[17-19]

In SJS/TEN the barrier function of the skin is lost due to full-thickness epithelial necrosis. Hence, disturbance of fluid, protein, and electrolyte balance leading to hypovolaemic shock and local and systemic infection with the threatening of sepsis, often leading to multi-organ failure, are the most important causes of death. The main point in dealing with SJS/TEN patients is to restore the barrier function of the skin and mucosae as quickly as possible and in the meantime prevent the effects of this barrier loss.

Knowledge of the treatment of SJS/TEN rests greatly on anecdotal observations, empirical experience and retrospective studies. Apart from direct withdrawal of the culprit drug and supportive care, there are no generally accepted guidelines for the specific treatment of SJS/TEN, and few controlled clinical trials have been performed due to the rarity and severity of the disease.[5,19] Several specific treatment options have been proposed on theoretical grounds. Some with promising results and others, e.g. thalidomide, with increased mortality, possibly due to paradoxically enhanced TNF-α production.[4,19] The supposed rationale for IVIG is its capacity to inhibit activation of the death receptor by Fas-blocking antibodies, but its clinical results were contradictory.[3,5,17,20,21] The use of corticosteroids in SJS/TEN is controversial.[7-10,22,23] The precise action of corticosteroids in inflammatory diseases is still not well understood. They have pleomorphic immune-modulating effects, e.g. through inhibition of numerous cytokines.[10] Nowadays the use of corticosteroids in SJS/TEN is generally not advocated because of the possibility of delayed healing and the risk of infection.[7,9,23] However, this opinion is based on only a few case series. Moreover, some cases in which it was stated that a better outcome was related to avoidance of corticosteroids had in fact taken corticosteroids for a mean of 3.5 days prior to referral. The general negative opinion of corticosteroids is probably because they are often given too late, in too low a dose, and for too long during the process. During the healing phase corticosteroids may indeed impair wound healing and promote sepsis. However, short courses of high-dose corticosteroids in early SJS/TEN have a good rationale, as immune mechanisms are

directly responsible for the cascade of events leading to apoptosis. Hence, we challenged the general opinion of corticosteroids being detrimental in the treatment of SJS/TEN.

Dexamethasone is a potent glucocorticoid (about 7 times as potent as the same dose of prednisolone) with a continuous action level, due to its relative long biological half-life (36–54 h). It has pleomorphic effects on the immune system and may inhibit epidermal apoptosis by several mechanisms: inhibition of T-cell activated apoptosis by suppression of various cytokines such as TNF-α; inhibition of interferon-γ induced apoptosis; and inhibition of Fas-mediated keratinocyte apoptosis.[10,24]

We gave DPT 1.5 mg/kg i.v. in 30–60 min on 3 consecutive days, thus avoiding long-term use of corticosteroids. Cyclophosphamide, added in the pemphigus regimen to prevent relapses, was omitted after patient 4 (see table 2), as relapses are not to be expected after withdrawal of the culprit drug. We saw no significant change in outcome and healing time.

Patients 5 and 7 had metastatic brain tumours, and patient 9 had systemic lupus erythematosus, for which they chronically received corticosteroids. These patients developed the SJS/TEN reaction after a longer lag time (time between first drug administration and first blister). This phenomenon has been described previously;[22] however, in patients 5 and 7 it might also be attributed to the culprit drug phenytoin, known for its potentially long lag time. Leukopaenia, regularly encountered in TEN, occurred in patients 5 and 1, in the latter neutropaenia was also present. Both patients experienced sepsis and HSV infection, probably attributing to delayed wound healing.

The efficacy of DPT was evaluated according to arrest of further epidermal or mucosal detachment, healing time in days, outcome and sequelae. The patients stabilized after an average of 2.3 days, while total re-epithelialization was reached after 13.9 days. Despite SCORTEN predicting a mortality of 4 patients, only one died. Serious late sequelae of the mucosae, especially of the eyes were not found.

Comparison with published results is difficult. Most records of therapeutic trials in TEN are case series without controls. We calculated SCORTEN as validated predictive score for the outcome in SJS/TEN.

In a large, multi-centre, epidemiological study the average period for stabilization was 4 days for SJS and 5.8 days for TEN. Healing was almost complete 20–30 days after hospitalization.[25] In another study, therapy with IVIG was started 4.1 days after the start of the disease and healing was complete 18 days after admission. SCORTEN predicted 8.2 deaths, while 11 actually occurred.[3] The authors concluded IVIG could not be recommended as a standard treatment for SJS/TEN. On the other hand, several IVIG studies mention surprisingly short periods of stabilization and/or healing.[20,21] In interpreting these results, one should also consider the time-lapse before treatment is started, as without treatment the period of progression may last 7–10 days.[19,25] Starting treatment late in the process implies that it is difficult to measure the effect of treatment on stabilization. Since we started quite early, we believe from our data that DPT did

result in a relatively quick stabilization and healing and suggest that DPT may even have halted the process of apoptosis.

Although the results of this study bear no statistical relevance due to the small number of patients, we conclude that short-term DPT, given at an early stage of the disease, may contribute to a reduced mortality rate in SJS/TEN without increasing healing time. A larger controlled trial is warranted in order to investigate further the use of DPT in SJS/TEN.

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3

Stevens-Johnson syndrome and toxic epidermal necrolysis in patients with lupus erythematosus: A descriptive study of 17 cases from a national registry and a review of the literature.

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Summary

Background: Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions with high morbidity and mortality. Some expressions of lupus erythematosus (LE) may cause enormous difficulties in differentiating them from SJS and TEN by showing large areas of sheet-like epidermal necrosis.

Objective: To evaluate clinically and histopathologically probable or definite cases of SJS/TEN with a history of systemic or other LE [(S)LE].

Methods: This was a retrospective analysis of validated cases of SJS/TEN with a history of (S)LE, based on a large population-based national registry.

Results: Among 1366 patients with SJS/TEN, 17 with a sufficiently documented history of (S) LE and representative histological material could be identified, suggesting a considerable over-representation of LE in patients with SJS/TEN. Eight of these showed clinically and/or histopathologically some LE-characteristic features interfering with the diagnosis of SJS/TEN. Differentiation could be elaborated on clinical and histopathological grounds: four patients were classified as SJS/TEN with a preceding (S)LE exacerbation and/or LE-typical histopathological features, and four as 'TEN-like' (S)LE.

Conclusion: Most patients with SJS/TEN and a history of (S)LE demonstrate clinical and histopathological properties allowing clear differentiation. However, occasionally acute cutaneous manifestations of (S)LE and SJS/TEN can be phenotypically similar, caused by extensive epidermal necrosis. Although no feature by itself is conclusive, a combination of recent (S)LE exacerbation, evident photodistribution, annular lesions and absent or only mild focal erosive mucosal involvement may favour LE over SJS/TEN clinically. Histopathologically, in particular, junctional vacuolar alteration, and the presence of solitary necrotic keratinocytes at lower epidermal levels, combined with moderate to dense periadnexal and perivascular lymphocytic infiltrates with a variable presence of melanophages, and mucin point to a LE-related origin.

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions (SCAR), mainly caused by drugs but also related to infections and unidentified causes. They are characterized by an acute onset of erythema with detachment of the epidermis and epithelia of mucous membranes resulting in extensive areas of denuded skin.[1,2] Classification of SJS/TEN is based on three clinical criteria: the pattern of individual skin lesions, their distribution and the maximum extent of epidermal detachment.[1] Atypical target lesions and/or erythematous or purpuric macules are present. Detachment of < 10% of the body surface area (BSA) is defined as SJS, 10–30% as SJS/TEN-overlap and > 30% as TEN.[1,2] SJS and TEN are considered to be severity variants of the same disease entity with SJS being the milder and TEN the most severe form.[3] In contrast, erythema multiforme with mucosal involvement, also called erythema multiforme majus (EEMM), which for a long time has been considered to be SJS, presents with typical target lesions mainly on the limbs. Both entities can be separated in more than 90% of the cases.[4,5] The mean age for SJS/TEN ranges between 48·2 and 53·4 years (range 1–98), and both sexes are affected in almost equal distribution but with a female preponderance in SJS/TEN-overlap.[2,5] SJS/TEN is rare, with one to two cases per million inhabitants per year, and causes high mortality, exceeding 40% for TEN, and, frequently, long-lasting disability.[2,6]

Histopathologically, the common pattern of SJS/TEN and EEMM is that of erythema multiforme. Early lesions show mostly sparse superficial perivascular and interstitial lymphocytic infiltrates, some lymphocytes at the dermoepidermal junction (DEJ), and necrotic keratinocytes (etymologically more correctly keratocytes) scattered throughout the lower epidermis and, sometimes, the upper part of the infundibular epidermis and eccrine ducts. Additionally, in fully developed lesions, subepidermal vesiculation appears secondary to extensive necrotic keratinocytes, resulting in confluent epidermal necrosis. The cornified layer retains its basket-weave pattern.[7,8]

By contrast, lupus erythematosus (LE) is a common autoimmune disease.[9,10] Diagnosis relies on clinical, histopathological and serological criteria. Cutaneous and systemic manifestations of LE are different clinical expressions of the same underlying autoimmune process.[9] Cutaneous manifestations in LE are very heterogeneous, varying from discoid atrophic erythematosquamous plaques to generalized maculopapular erythematous rashes.[11] Symptom-based diagnostic classification divides LE into cutaneous-limited LE, intermediate LE and systemic LE (SLE). Morphological classification of specific cutaneous manifestations distinguishes acute cutaneous LE (ACLE), subacute cutaneous LE (SCLE) and chronic cutaneous LE (CCLE), with subtypes.[12] The incidence of SLE among populations of European descent strongly varies from 1·8 to 7·6 cases per 100 000 persons per year, while the prevalence varies from 17 to 48 per 100 000.[13,14] In further studies, incidence rates for male and female subjects were calculated to be 3·7 and

45·4 cases per 100 000 per year, respectively.[15] The highest incidence is mentioned for women of child-bearing age. Cutaneous variants of LE are two to three times more frequent than SLE.[10]

Cutaneous manifestations of SLE or other LE [(S)LE] demonstrate a broad histopathological spectrum.[11,16] Early findings include sparse superficial perivascular lymphocytic infiltrates, neutrophils and sometimes nuclear dust immediately beneath the DEJ. Few individual apoptotic keratinocytes, focal vacuolar alteration of basal cells and extracellular mucin deposition in the reticular dermis may be found. Fully developed lesions show moderately dense perivascular and periappendageal lymphocytic infiltrates in the papillary and reticular dermis, and abundant mucin deposits in the latter. There is focal or continuous epidermal thinning, smudged appearance of the DEJ with vacuolar degeneration of basal cells, individual necrotic keratinocytes and a thickened basement membrane zone (BMZ). Moreover, compact orthokeratosis, follicular horny plugs and melanophages in the upper dermis may be found. In late lesions, inflammatory cell infiltrates subside and there is follicular and epidermal atrophy with loss of rete ridges, vacuolar alteration of basal cells, marked thickening of the BMZ and mild interface dermatitis.[7] However, SCLE is characterized by rather cell poor infiltrates, without follicular plugging and severe epidermal atrophy. Furthermore, hyperkeratosis, BMZ thickening and pigmentary incontinence are less pronounced.

Some clinical expressions of LE may cause extreme difficulties in differentiation from SJS/TEN. Large areas of sheet-like epidermal cleavage may develop, resulting in TEN-like changes in both cutaneous-limited LE and SLE. Overlap of clinical and histopathological findings in SJS/TEN and vesiculobullous LE manifestations have led to the assumption of 'TEN-like LE' or 'LE-associated TEN'.[17-24]

This is the first clinical and histopathological evaluation of probable or definite cases of SJS/TEN with a history of (S)LE conducted in a nation-wide, population-based registry.

Patients and methods

German registry of severe skin reactions

For this analysis, cases of SJS/TEN, ascertained and validated by the German registry were used. Cases are actively detected in a network of approximately 1700 hospitals including all departments of dermatology and paediatrics, burn units, and departments of internal medicine with intensive care facilities in Germany. Each patient meeting inclusion criteria for potential SJS/TEN is seen by a physician investigator of the registry centre, and interviewed using a standardized disease-specific questionnaire. The interview contains questions regarding demographics, current illness, morphological and biological data, recent and past medical history including (S)LE and other autoimmune diseases, prior infections, use of medication including indication, and earlier adverse drug reactions. A dermatological expert committee reviews all cases, following a structured scoring system, using clinical data, photographs,

distribution drawings and histopathological reports/photographs, but blinded for drug exposure and other risk factors. Based on the consensus definition published by Bastuji-Garin *et al.* in 1993, cases are classified as 'definite', 'probable' or 'possible' SJS/TEN or are excluded.[1] In a minority of about 7–8%, a definite differentiation between SJS and EEMM is not possible.[2,4,5] As patients with SJS/TEN require hospitalization, only very few patients should be missed. Thus, the registry is considered to be exhaustive for detection of SJS/TEN in Germany.[25] Since 2003 all cases of the German registry are included in the RegiSCAR-project (an international registry of SCAR and collection of biological samples) which is coordinated by the German registry (this concerns cases 13, 14, 15, 16 and 17 which correspond to the RegiSCAR-interview numbers 9150175, 9160189, 9160252, 9170392 and 9160264, respectively).[25]

Selection of cases with lupus erythematosus among registry cases of Stevens–Johnson syndrome/toxic epidermal necrolysis and retrieval of additional data

All consecutive cases from 1990 to 2006 validated as probable or definite SJS/TEN with an affirmative answer to SLE in their history were selected. In addition, the database was searched for any mention of (S)LE in the free text. To substantiate the diagnosis of (S)LE, the treating physician was asked for additional documents, including discharge letters, hospital charts, laboratory results including histopathology and immunofluorescence, and other information from the general practitioner and from specialists. Patients with cutaneous LE or fulfilling the criteria of the American College of Rheumatology (ACR) for SLE were selected for further histopathological evaluation.

Clinical investigation

General, clinical and histopathological data on SJS/TEN were collected prospectively for case validation, whereas details for substantiation of (S)LE were gathered retrospectively for this study including the request for skin biopsy material. Clinical characteristics at the event included age, sex, duration and type of LE, substantiation of LE diagnosis, immunosuppressive therapy before the event, pre-existing (muco)cutaneous lesions, (muco)cutaneous involvement at the time of the event, and outcome. Skin and mucous membrane involvement as well as photodistribution were evaluated on clinical photographs and distribution drawings. In a second and independent step, the index-day, i.e. onset of the reaction, which is usually the appearance of first cutaneous or mucosal symptoms, sometimes fever and malaise 1 day before, is determined for each validated case. Drug causality was evaluated based on an algorithm including relevant exposure time before the index-day, potential earlier reactions to the drug, potential alternative causes and drug notoriety.[5,6]

Histopathological investigation

For all selected cases, relevant slides or paraffin blocks were requested from the treating departments; cases without an informative biopsy were excluded. Haematoxylin and eosin sections, including recuts, were independently examined by two of the authors (M.Z. and S.H.K.), using a predetermined panel of histopathological criteria considered diagnostic for LE and SJS/TEN (**Table 1**). In case of discordant results, consensus was reached after discussion. Histopathological changes were interpreted as suggestive for LE if at least four LE-characteristic features were observed. Histopathological features were compared against history and clinical information at the time of the event, including clinical photographs and drawings, and course of the disease.

Table 1. Histopathological features, typical for lupus erythematosus (LE) and Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN)

Epidermal changes	LE-typical: ortho-/hyperkeratosis, intrafollicular hyperkeratosis, atrophic epidermis, solitary necrotic keratinocytes in the lower epidermal layers
	SJS/TEN-typical: multiple necrotic keratinocytes within the entire epidermis
Changes at the dermoepidermal junction	LE-typical: presence of vacuolar degeneration, thickened basement membrane zone
	SJS/TEN-typical: necrotic keratinocytes dominate the junctional changes, vacuolar changes being absent or present only sparsely
Dermal changes, including characteristics of the inflammatory infiltrate	LE-typical: moderate or dense, superficial and deep lymphocytic infiltrate, presence of melanophages, plasma cells or mucin
	SJS/TEN-typical: sparse, superficial lymphocytic infiltrate
Involvement of adnexa (hair follicles and sweat glands)	LE-typical: periadnexal lymphocytic infiltrates, basal vacuolar degeneration at infundibula and solitary necrotic keratinocytes
	SJS/TEN-typical: solitary or multiple necrotic keratinocytes possible, however without considerable inflammatory infiltrate

Statistical analysis

Statistical analysis was done on a descriptive and analytical basis. Data were analysed using MS Excel Data Analysis.

Literature research of Stevens–Johnson syndrome/toxic epidermal necrolysis (TEN) in patients with lupus erythematosus (LE) and TEN-like LE

To allocate reports of a possible combination of (S)LE and SJS/TEN, a Medline search was conducted, finalized in November 2009, using combinations of the preferred terms of lupus, lupus erythematosus, SLE, or LE on one hand and Stevens–Johnson syndrome, SJS, toxic epidermal necrolysis, TEN or Lyell on the other hand. Two reviewers (M.Z., S.H.K.) independently screened all the articles on title/abstract. The reference lists of these articles were screened for additional studies. Final selection was based on assessment of the full text of the article with a sufficient description of both (S)LE and SJS/TEN. Data extraction was independently performed by two reviewers (M.Z., S.H.K.). In case of discordant results, consensus was reached after discussion.

Results

Inclusion

Among a total of 2590 cases, 1366 had been validated as definite or probable SJS/TEN, 27 of which had a history of (S)LE. Because of insufficiently documented LE diagnosis, six cases were excluded. Out of the remaining 21 cases, representative histopathological slides or sufficient paraffin material were provided for 17 patients: one EEMM/SJS, seven SJS, six SJS/TEN-overlap and three TEN.

Clinical characteristics

The clinical characteristics of these 17 patients are summarized in **Table 2**. All cases are represented by patients of European descent. The average age was 49·2 years (range 22–80 years); two patients were male (12%) and 15 female (88%). Mortality rate was 35% (six of 17). SLE was concomitantly present in 13 patients, two had cutaneous-limited LE, one SCLE and, in one, diagnosis of either cutaneous-limited LE or SLE was not clarified. Median duration of (S)LE before occurrence of SJS/TEN was approximately 3 years (varying between several weeks and 20 years). In one patient, duration was not mentioned and, in a further patient, SLE was diagnosed concomitantly with SJS. Positive anti-Ro or anti-La antibodies were mentioned in six of 17 cases. Thirteen patients were on significant systemic immunosuppressive therapy prior to their diagnosis of SJS/TEN (76%); the majority of these (10/13; 77%) used a combination of systemic glucocorticosteroids and another immunosuppressive drug such as azathioprine, cyclophosphamide, leflunomide and chloroquine. The median time from the index-day to the day of maximum blisters and erosions was 7 days (range 2–18). Seven patients experienced

an exacerbation of LE prior to the event, five showed lesions compatible with LE, four of these evidently with photodistribution (**Fig. 1a–c**; case 6). Drugs potentially causal for SJS/TEN could be identified in 15 of 17 patients (88%), one drug in five cases, two in eight and three in two cases.

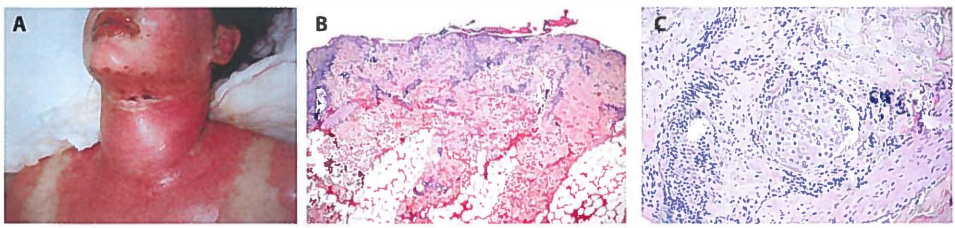

Figure 1. Case 6. A female patient with 'Stevens–Johnson syndrome/toxic epidermal necrolysis-like' systemic lupus erythematosus. (a) Extensive erythema with large areas of erosion, erosive cheilitis and accentuation on sun-exposed skin. (b) Complete epidermolysis with only residual intact epithelium of acrosyringia; moderate, superficial and mid-dermal, perivascular and periadnexal lymphocytic infiltrates [haematoxylin and eosin (H&E); original magnification × 40]. (c) Vacuolar alteration at the dermoepidermal junction of a sebaceous gland with solitary necrotic keratinocytes associated with lymphocytes (H&E; original magnification × 200).

Table 2. Clinical characteristics of re-evaluated cases

No.	Age (years)/ sex	Diagnosis/ event	Duration and type of LE	LE criteria clinically and previous changes	LE characteristic laboratory values	Immunosuppressive therapy before event[a]	Skin lesions before event	Time period[b]	Skin involvement	LE typical photodistribution	Involvement of palms, soles	Involvement of mucous membranes	Outcome	Potential cause of SJS/TEN
1	45/F	01/94 definite SJS	01/92 SCLE 1995 SLE	08/93 skin lesions after sun exposure, 11/93 LE exacerbation, suspected autoantibody haemolysis and thrombopenia, suspected vasculitis; 1995 autopsy, vasculitis due to LE with pancreas, renal and central nervous system involvement	ANA 1 : 320, ANA (Hep2) quantitative speckled 1 : 1280, anti-Sm positive, C4 decreased, DIF: no lupus band	Yes (p, c)	No	7	Atypical targets flat, spots widespread	No	Soles	Oral	Discharge	Multiple medication use;[c] possible doxycycline, ciprofloxacin
2	76/F	01/93 probable TEN on large erythema	1992 SLE	LE-associated autoimmune hepatitis	1992 ANA 1 : 160, SMA 1 : 160	Yes (p)	No	2	Erythema with large epidermal sheets	No		Oral, eyes	Discharge	5 different long-term drugs, none could be identified as the culprit
3	23/F	04/96 probable SJS	1987 SLE	Photosensitivity, 1986/87 recurrent fever, 1987 skin lesions and polyarthritis, skin biopsy vasculitis, later increasing skin lesions with scarring and contractures, 1996 cerebral vasculitis with hemiparesis, pleurisy, pericarditis, interstitial nephritis, malnutrition	1996 ANA 1 : 2560, anti-dsDNA 136·7 kU L^{-1}, leucopenia	Yes (p,c)	No	3	Spots widespread	No	Palms, soles	Lips, eyes	Discharge	Multiple medication use; possible imipenem, tramadole
4[d]	52/F	07/01 definite SJS/TEN	02/2001 SCLE/SLE	Photosensitivity, annular scaling skin lesions since 02/2001 mainly on sun-exposed areas, long-lasting liver function disturbances	2001 ANA 1 : 1280, SS-A/Ro-52, SS-A/Ro-60 and SS-B/La positive, C4 decreased, anaemia, leucopenia	Yes (d)	~5 months prior event increasing red macules, first blistering ~6 weeks prior to event	10	Spots widespread, patchy	No		Oral	Death	Possible valaciclovir, herpes labialis
5[d]	36/F	10/99 definite SJS	1994 SLE	N.m.; at time of the event only mentioned 'no complaints concerning previously diagnosed LE'	N.m.	No	No	4	Atypical targets raised, atypical targets flat widespread	No	Palms, soles	Lips, oral, eyes	Discharge	Probable co-trimoxazole, possible amoxicillin

No.	Age (years)/ sex	Diagnosis/ event	Duration and type of LE	LE criteria clinically and previous changes	LE characteristic laboratory values	Immunosuppressive therapy before event[a]	Skin lesions before event	Time period[b]	Skin involvement	LE typical photodistribution	Involvement of palms, soles	Involvement of mucous membranes	Outcome	Potential cause of SJS/TEN
6[d]	31/F	06/00 definite SJS/TEN	1996 SLE	Polyserositis, haematological, cardiac involvement; 12 cyclophosphamide courses 1997/98	2000 ANA 1 : 1280, anti-Ro 1412·7 positive, anti-La 154·6 borderline; antihistone 42·5 positive; anti-dsDNA positive; anaemia, leucopenia, C3 decreased; DIF: fibrin band-like, C3 granular at blister floor	Yes (p, a)	Over ~ 6 weeks prior to event development of erythema face, decolleté and upper arms after sun exposure	11	Spots widespread, erosions in photodistribution	Face, décolleté, upper back, extensor site of arms	Localized bulla sole	Lips, oral, anal	Discharge	Possible rofecoxib, diclofenac
7	31/F	06/97 definite SJS/TEN	1988 SLE	1988 deep venous leg thrombosis and positive lupus anticoagulant, 1995 arthralgias, photosensitivity, fatigue, hair loss, chronic lymphadenitis with high-grade lymphofollicular hyperplasia like in RA or collagenosis; 1997 cerebral LE vasculitis (MRI and CT), suspicion of cardiac LE involvement	1996 direct Coombs test: anti-erythrocyte autoantibodies, cold reactive erythrocyte alloantibodies; 1997: C3 borderline	Yes (p, l, ch)	No (lesions did start on the face)	18	Spots widespread	No		Lips	Discharge	Probable co-trimoxazole, possible hydroxychloroquine
8	22/M	08/97 definite SJS	04/1997 SLE	Skin lesions, photosensitivity, mesangioproliferative glomerulonephritis, arthritis, recurrent fever	ANA 1 : 800, anti-Sm and anti-RNP positive, anti-dsDNA positive, leucopenia, thrombopenia, CH50 decreased	Yes (p,c)	No; after 1 week sun exposure, erythema face and trunk	6	Spots widespread	No	Palms, soles	Lips, oral, genital	Discharge	Probable allopurinol
9[e]	50/F	08/98 definite EEMM/SJS	1998 suspected SCLE	Organic psychosis attributed to LE or steroid induced	07/1998 ANA elevated, anti-Ro 1 : 1296 (09/98 anti-Ro negative), antiphospholipid discrete, elevated creatinine, DIF negative	Yes (p, ch)	First EEM-like skin lesions about 6 weeks prior to the event (SCLE suspected)	6	Typical and atypical targets raised, spots widespread	No		Erosive mucosal involvement (oral slightly, genital and anal)	Discharge	Possible hydroxychloroquine

No.	Age (years)/ sex	Diagnosis/ event	Duration and type of LE	LE criteria clinically and previous changes	LE characteristic laboratory values	Immunosuppressive therapy before event[a]	Skin lesions before event	Time period[b]	Skin involvement	LE typical photodistribution	Involvement of palms, soles	Involvement of mucous membranes	Outcome	Potential cause of SJS/TEN
10	45/F	01/99 definite TEN	1980 SLE	Anti-phospholipid syndrome, involvement of skin, heart, lung, kidney; last exacerbation 1995 with extensive skin and liver involvement	Anti-phospholipid, elevated transaminases	Yes (p, a)	No	7	Atypical targets flat, spots widespread	No	Palms, soles	Lips, oral	Death	Possible amoxicillin, diclofenac
11[d]	78/F	02/99 probable SJS	CLE	N.m.	DIF negative	No	No	12	Atypical targets flat, spots widespread; in parts annular, patchy, crusted	Yes			Death	Possible sertraline, amitriptyline
12	59/F	12/02 definite TEN	For a few weeks SLE	2002 for a few months fever and exanthema, pulmonary infiltrate, antibiotics not effective, after prednisolone immediately afebrile and improved general condition	11/2002 high positive anti-dsDNA, anti-SS-A, slightly increased transaminases, leucopenia, anaemia, positive RF, C4 decreased	Yes (p, a, c)	No	10	Spots widespread	No	Palms	Lips	Death	Multiple medication use; possible metamizole (more likely), piperacillin/tazobactam
13[d]	67/F	08/04 probable SJS	2001 suspected CLE, 2003 questionable SLE; 2005 proven SLE	2001 acute dermatitis sun-exposed skin; 2003 admission with acute LE exacerbation; 2005 (after SCAR) SLE, recent acute exacerbation with severe skin involvement (exfoliative dermatitis)	Positive ANA, positive nDNA	Yes (p)	1 month prior to exacerbation of LE with cutaneous lesions face, shoulders, back	10	Type of targets unknown, in parts annular, crusted	Yes			Discharge	Multiple medication use; possible cefazolin, metamizole, amoxicillin/clavulanic acid
14	80/F	09/04 definite SJS	2004 possible SLE	During SCAR erythema periungual, cheeks; mucosal erosions and pericardial fluid	ANA 1 : 640, anti-dsDNA 271 (< 30), *Crithidia*-ab 1 : 10 (< 1 : 10), SMA 1 : 160 (< 1 : 40)	No	No	3	Type of targets unknown, mostly crusted	No	Palms, soles	Lips, oral, eyes, nasal	Discharge	Probable allopurinol

No.	Age (years)/ sex	Diagnosis/ event	Duration and type of LE	LE criteria clinically and previous changes	LE characteristic laboratory values	Immunosuppressive therapy before event[a]	Skin lesions before event	Time period[b]	Skin involvement	LE typical photodistribution	Involvement of palms, soles	Involvement of mucous membranes	Outcome	Potential cause of SJS/TEN
15[e]	30/M	02/05 definite SJS/TEN	1994 CLE, 2001 SLE	1 month before SCAR acute exacerbation LE; photosensitivity, butterfly erythema, discoid skin lesions, diffuse generalized pain, emotional lability with aggression attributed to LE, critical-illness-polyneuropathy	ANA 1 : 800, anti-SS-A, anti-SS-B positive; proteinuria, pathological creatinine clearance, leucopenia, thrombocytopenia, anaemia	Yes (p, a, c)	1 month prior to acute exacerbation of LE with cutaneous lesions face, trunk, feet	7	Atypical targets flat, spots widespread	No	Palm, soles	Lips, oral, eyes	Discharge	Multiple medication use; possible phenoxymethylpenicillin, etoricoxib, metamizole
16	78/F	03/06 definite SJS/TEN	2005 CLE or SLE	2005 suspected acute LE-nephritis in longstanding not systemic LE, skin: healing small blisters back and arms, erythema right face	ANA: weakly positive, ENA 1·0 (< 1·0), proteinuria, creatinine clearance 27·8 mL min ^{1}, anaemia, RF 25 (< 15), IgM 19·45 (< 15), Waaler–Rose test 1 : 1280 (< 1 : 40)	No	No	4	Spots widespread	No	Soles	Lips, oral, eyes, nasal	Death	Multiple medication use; possible allopurinol
17[d]	34/F	03/05 definite SJS/TEN	1985 SLE	01/2005 malar rash with partially erosive lesions on the face, fingertips and toes, depression	01/2005 ANA 1 : 5120, dsDNA > 200, anti-Ro 22·7, anti-Sm > 200, anti-RNP > 200, leucopenia, anaemia, massive proteinuria, total complement, C3 and C4 decreased	Yes (p, a, c)	Exacerbation of LE with characteristic cutaneous lesions (face, extremities) for several weeks	4	Atypical targets flat, spots widespread	No	Palms, soles	Lips, oral, eyes	Death	Multiple medication use;[c] none could be identified as the culprit

ANA, antinuclear antibodies; CLE, cutaneous LE; CT, computed tomography; DIF, direct immunofluorescence; dsDNA, double-stranded DNA; EEM, erythema multiforme; EEMM, EM majus; LE, lupus erythematosus; MRI, magnetic resonance imaging; N.m., not mentioned; RA, rheumatoid arthritis; RF, rheumatoid factor; RNP, ribonucleoprotein; SCAR, severe cutaneous adverse reaction; SCLE, subacute cutaneous LE; SJS, Stevens–Johnson syndrome; SLE, systemic LE; SMA, smooth muscle antibodies; TEN, toxic epidermal necrolysis. [a]Therapy: a, azathioprine; ch, chloroquine; c, cyclophosphamide; d, dexamethasone; l, leflunomide; p, prednisolone/prednisone. [b]Time period index-day to day of the maximum blisters/erosions. [c]Multiple medication use ≥ 10 different medications within 4 weeks before the index-day. [d]Cases with histopathological features of LE. [e]Cases with clinical features of LE.

Histopathological characteristics

Detailed histopathological findings are listed in **Table 3**. Characteristic features of SJS/TEN including a normal basket-woven cornified layer, scattered necrotic keratinocytes often resulting in subepidermal vesiculation and confluent necrosis of the surface epidermis, and a mostly sparse superficial perivascular and interstitial lymphocytic infiltrate were found in 10 out of 17 patients. Sometimes secondary changes were present such as focal parakeratosis, serum crusts or neutrophilic granulocytes in the horny layer or ulcerated surface.

As expected, in all biopsies, necrotic keratinocytes up to complete necrosis were present throughout the entire epidermis. Nevertheless, six biopsies were interpreted as compatible with LE, based on four or more histopathological LE-characteristic criteria such as vacuolar alteration at the DEJ, presence of solitary necrotic keratinocytes at lower epidermal levels with analogous changes of acrosyringia and follicular infundibula combined with periadnexal lymphocytic infiltrates, thickened BMZ and moderate to dense superficial and deep dermal lymphocytic infiltrates with variable presence of plasma cells, melanophages and mucin (**Fig. 2a–d**; case 5). Two of these biopsies met seven, three met five and one met four of the listed LE criteria. In five of six cases vacuolar degeneration at the DEJ was present, a feature found only in two cases not suggestive for LE. A thickened basement membrane was found in only one case, a phenomenon explainable by the acuteness of the evaluated cases, as a thickened basement membrane is found only in long-standing, mostly discoid LE plaques. Moreover, we noticed the absence of plasma cells in all except one case.

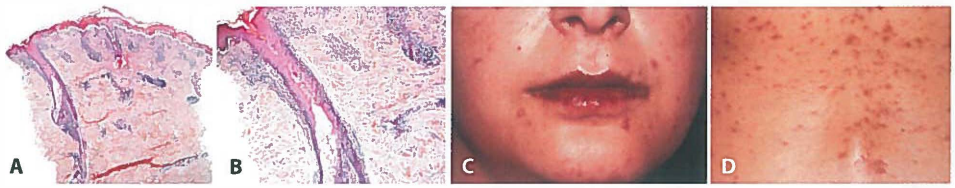

Figure 2. Case 5. A female patient with Stevens–Johnson syndrome showing concomitant histological features of lupus erythematosus. (A) Moderate, superficial and deep, perivascular and periadnexal infiltrates, extensive epidermolysis; the blister roof is completely necrotic [haematoxylin and eosin (H&E), original magnification × 40]. (B) Epidermis adjacent to the areas of epidermolysis shows vacuolar alteration at the dermoepidermal junction, solitary necrotic keratinocytes at lower epidermal levels with analogous changes at follicular epithelium combined with periadnexal lymphocytic infiltrates, and moderate to dense superficial and deep perivascular lymphocytic infiltrates with presence of melanophages (H&E; original magnification × 100). (C) Erythematous erosive papules on the face with erosive cheilitis. (D) Disseminated erythematous, in parts erosive, papules on the trunk.

Table 3. Histological characteristics of re-evaluated cases

	Case no.																
	1	2	3	4[a]	5[a]	6[a]	7	8	9	10	11[a]	12	13[a]	14	15	16	17[a]
Hyperorthokeratosis	0	0	**1**	0	0	0	0	0	0	0	**1**	0	0	0	0	0	0
Intrafollicular hyperkeratosis	0	0	0	0	**1**	0	0	0	0	0	0	0	**1**	0	0	0	0
Atrophic epidermis	0	**1**	0	**1**	0	0	0	0	0	0	**1**	0	**1**	0	0	0	0
Solitary necrotic keratinocytes within lower epidermis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Multiple necrotic keratinocytes within entire epidermis (1)/complete epidermal necrosis (2)	1–2	1	1–2	1–2	1	1–2	1–2	1–2	1–2	1–2	1–2	1–2	1–2	1	1	1	1–2
Vacuolar degeneration	0	0	**1**	**1**	**1**	cn.e.	0	**1**	0	0	**1**	0	**1**	0	0	0	**1**
Thickened basement membrane	0	0	0	**1**	0	cn.e.	0	0	0	0	0	0	0	0	0	0	0
Lymphocytic infiltrate (1, sparse; 2, moderate; 3, dense)	1	**2**	1	**2**	**2**	**2**	1	1	1	1	1	1	**2**	1	1	1	**2**
Lymphocytic infiltrate (1, superficial; 2, superficial and deep)	1	1	1	**2**	**2**	**2**	1	1	1	1	1	**2**	1	1	1	1	**2**
Plasma cells	0	0	0	**1**	0	0	0	0	0	0	0	0	0	0	0	0	0
(Peri)-adnexal involvement (hair follicles) (necrotic keratinocytes and lymphocytic infiltrate)	i.n.k., n.c.i.	cn.e.	0	0	**1**	**1**	i.n.k., n.c.i.	i.n.k., n.c.i.	0	i.n.k., n.c.i.	0	0	i.n.k., n.c.i.	0	i.n.k., n.c.i.	i.n.k., n.c.i.	0
(Peri)-adnexal involvement (sweat glands) (necrotic keratinocytes and lymphocytic infiltrate)	0	cn.e.	0	0	**1**	**1**	0	0	0	0	0	a.n.k., n.c.i.	0	0	0	0	0
Melanophages	0	**1**	0	0	**1**	0	0	0	0	0	**1**	**1**	**1**	0	0	0	0
Mucin	0	0	**1**	**1**	0	**1**	0	0	0	0	(**1**)[b]	0	0	0	0	0	**1**
Direct immunofluorescence	cn.e.	cn.e.	cn.e.	cn.e.	cn.e.	Linear fibrin, granular C3 blister roof	cn.e.	cn.e.	cn.e.	cn.e.	cn.e.	cn.e.	negative	cn.e.	cn.e.	cn.e.	cn.e.

Bold face indicates positive lupus erythematous (LE) features. 0, absent; 1, present (if not further specified); cn.e., cannot be evaluated; i.n.k., infundibular necrotic keratinocytes; a.n.k., acrosyringeal necrotic keratinocytes; n.c.i., no considerable inflammatory infiltrate. [a]Cases with more than four histopathological features of LE. [b]Pale section.

Cases of Stevens–Johnson syndrome/toxic epidermal necrolysis in patients with lupus erythematosus in the literature

A total of 14 publications with SJS or TEN in the context of (S)LE have been published between 1961 and 2009.[26-39] Of these, 11 publications, including 12 patients and 14 episodes contained sufficient data for evaluation (**Table 4**).[26,28-36,39] All concerned female subjects, median age 29 years (range 9–76). The authors interpreted nine episodes as SJS and five as TEN. In one, SJS and TEN subsequently appeared, while, in a child, recurrent SJS was reported. Clinical presentations were illustrated by representative photographs for eight episodes. Histopathology of the skin was performed in 10 and photodocumented in four episodes, of which three could not be interpreted because of very limited high-power details. SLE was diagnosed simultaneously with SJS or TEN in four episodes, (S)LE prior to the event in nine (range 11 months to 16 years, two not mentioned), and 5 months after the event in one. However, pre-existing LE-suspicious mucocutaneous lesions and/or systemic symptoms suggest that (S)LE in three of the simultaneous and in the later diagnosed case was already present at the event.

Six of nine patients with pre-existing SLE used corticosteroids, one additionally cyclophosphamide and another mizoribine. In all episodes, a potentially culprit drug for SJS/TEN was assigned, generally introduced or reintroduced within hours (three of 14), several days (two of 14), 'recently' (one of 14), 1–6 weeks (three of 14) and in 1–6 months (three of 14) prior to the event. One child used the medication 3·5 years before the first episode, followed by 3 years of mild recurrences and a second episode. In a second child the reaction occurred after 11 months.

Analysing the published data of these 14 episodes we concluded the following points. (i) Seven events could fit a diagnosis of SJS (or EEMM)[28,30,31,34] or TEN.[29,30,33] Although some aspects were presented fragmentarily, clinical pictures and precise descriptions did allow for diagnosis. (ii) The diagnosis of SJS or TEN could not be evaluated in five events, due to inconclusive clinical and histopathological description and/or pictures.[26,32,39] However, the recurrent cases are far more suggestive for EMM than for SJS.[26] (iii) In two reports the presentation was based on clinical and histopathological findings more likely to be related to (drug-induced) LE.[35,36]

Table 4. List of reported cases of Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) in patients with lupus erythematosus (LE) in the literature

			Activity of LE			TEN/SJS-features			Histology			
Author/reported SJS/TEN	LE-type/ duration	Age (years) /sex	Laboratory/clinically	Immuno-suppressive drugs	LE-specific skin lesions	Lesions/time of development	Localization	Mucous membrane involvementw	Description	Figure	Culprit drug(s)	Outcome
Rallison 1961[26]												
Patient 1												
First episode SJS	LE/simultaneously	11/F	LE cells negative	None	None	Fever, malaise; scattered bullous lesions (no photograph)/n.m.	Scattered	Mucous membrane erosions, conjunctivitis	Not performed	No	Trimethadione and phenobarbital for 3-5 years	9% eos, locally, stop drugs with mild recurrences during next 3 years
Second episode SJS	SLE?/3 years	14/F	LE cells pos, LE cells in the bone marrow aspirate, 8 months later lupus nephritis	None	Butterfly rash	Fever paronychia (no description of skin lesions)/n.m.	N.m. in detail (photo:circumscribed erythematobullous plaques on thigh)	Extensive oral, genital lesions, identified as recrudescence of SJS	Not performed	No	Mephobarbital/diphenylhydantoin and paramethadione for 3 years	15% eos, stop drugs with clearing of skin over next 6 months; at 8 months LE test normalized and diagnosis of lupus nephritis, cured 2 years later
Patient 2 SJS	SLE?/simultaneously	11/F	LE cells pos, histology: lupus glomerulitis 1 month later	None	Oral mucous membrane erosions over several months	Recurrent fever erythematous, bullous lesions in various stages over the body, developed for the first time during pneumonia	Generalized	Ulcerative lips, nasal and buccal mucosa	Not performed	No	Trimethadione, diphenylhydantoin 11 months, later phenobarbital	Stop drugs, initially improvement with antibiotics, after relapse cortisone 300 mg m^{-2} daily, after 3 weeks reduction resulting in exacerbation and additional 3 weeks cortisone, followed by reduction without difficulties, After 6 weeks cortisone LE cells negative 10 months after cessation cortisone free of lesions

			Activity of LE			TEN/SJS-features			Histology			
Author/reported SJS/TEN	LE-type/ duration	Age (years) /sex	Laboratory/clinically	Immuno-suppressive drugs	LE-specific skin lesions	Lesions/time of development	Localization	Mucous membrane involvemntw	Description	Figure	Culprit drug(s)	Outcome
Mendoza 1973[28] *SJS*	SLE/simultaneously	40/F	Simultaneously with the event lupus nephritis, anti-DNA negative, LE cells	Corticosteroid (for arthralgias)	Erythematosquamous, crusted lesions ears, depigmented macules face	Fever, erythematous oedema of eyelids, blepharitis, conjunctivitis/acute	Face, genitalia	Erosive cheilitis, erosions of oral mucosa, erosive colpitis	Not performed	No	2 months before acetylsalicylic acid, streptomycin, tetracycline	64 mg Deltisone and dose reduction, 6 weeks later worsening of lupus symptoms and increase to 128 mg Deltisone, patient died from cardiac fibrillation
Sayag 1980[29] *TEN*	SLE/after event	65/F	1 month before cardiopathy, increased ESR, cytopenias; after the event LE diagnosis based on prolonged fever, myalgia, pleurisy, pericarditis, LE cells, ANA 1 : 1000, anti-dsDNA	None	None	Fever, generalized purpuric erythematopapular, extensive epidermal detachment/rapid	Generalized	Ocular and oral mucous membranes involved	Complete epidermal necrosis, no inflammatory infiltrate, DIF (bullous lesion) linear homogeneous IgG, IgM, C3 at BMZ, later linear homogeneous IgG at BMZ in healthy skin	Detail only	Aprindine hydrochloride and clorazepate 4 days before the event	Dexamethasone 8-12 mg daily, then betamethasone/ prednisolone 15 mg kg^{-1} daily; discharge after 1 month (skin healed). Died several months later from tuberculosis
Burge 1985[30]												
First episode SJS	SLE/before event	73/F	History of cerebral and pulmonary LE, no further details reported	Prednisolone 15 mg	None	Erythematous rash/not reported	Face, trunk, limbs	Mouth ulcers, nasal crusting, genital erosions	Extensive vacuolar degeneration,individual necrotic keratinocytes, mononuclear cell infiltrate, coalescent necrosis of keratinocytes in roof of a subepidermal bulla, horny layer preserved	High-power detail of epidermis only	Phenytoin, 6 weeks before rash	Phenytoin stopped, prednisolone 60 mg daily; slowly improvement, discharge after 6 weeks

			Activity of LE			TEN/SJS-features			Histology			
Author/reported SJS/TEN	LE-type/ duration	Age (years) /sex	Laboratory/clinically	Immuno-suppres-sive drugs	LE-specific skin lesions	Lesions/time of deve-lopment	Localization	Mucous mem-brane involve-mentw	Description	Figure	Culprit drug(s)	Outcome
Second episode TEN		76/F		Predniso-lone 15 mg	None	Progressive erythema-tous rash, within 1 week. Blistering, peeling, scalded appearance	Trunk, arms, and palms (erythema)	Mouth ulcers, conjunctivitis	Confluent epidermal necrosis, subepidermal split	No	Recently tetracycline for chest infection	Prednisolone 60 mg daily, recovered fully, discharge after 2 months
Savill 1988[31] SJS	Active SLE/16 years	46/F	Presently 5 weeks malaise and weight loss, for 16 years recurrent fever, skin rashes, polyarthralgia, ANA > 1 : 320, DNA binding 52%, decre-ased complement, anaemia, leucope-nia, lymphopenia, active SLE with recent deteriorated renal function with proliferative glomeru-lonephritis	None	None	Fever, large ulcerone-crotic plaques, some with bullous changes/8 h after urography, target lesions	Extensor aspect of the limbs, buttocks, and trunk	Painful erosions of mouth and nares, nasal crusting	Severe lymphohistio-cytic infiltrate throughout the dermis, marked oedema, focal epidermal necrosis with subepidermal bulla forma-tion, DIF (lesional and nonlesional) linear IgM and C3 at BMZ	No	Iopamidol 8 h before the event	Dexamethasone high dose, later cyclophosphamide 70 mg daily added for 1 week. Patient died 6 weeks after admission from multiorgan failure
Moshfeghi 1993[32] TEN	SLE/15 years	31/F	Normal renal func-tion, otherwise not specified	Varying doses oral prednisone past 13 years	N.m.	Diffuse erythematous, painful, morbilliform rash, eroded bulla, ero-sions; few days later 'des-quamation' and positive Nikolsky; hospital day 4 further extent 'desqua-mation'/few days	Morbilliform rash on trunk, upper and lower extremities, face and palms, one bulla arm, one erosion labia, later 'desquama-tion' posterior thighs, back and arms	Desquamation lips with mini-mal crusting, no oral ulcerations, no eye- involve-ment	Skin necrosis with sloughing and subepi-dermal bullae, consistent with TEN	No	After 1st dose, ciprofloxacin 750 mg twice daily, prolonged use for 6 days (rash 1 year earlier after ciprofloxacin, resolving at drug discon-tinuation)	Parenteral followed by oral methyl-prednisolone and prednisone during hospital stay; recovered after prolonged hospi-talization

			Activity of LE			TEN/SJS-features			Histology			
Author/reported SJS/TEN	LE-type/ duration	Age (years) /sex	Laboratory/clinically	Immuno-suppressive drugs	LE-specific skin lesions	Lesions/time of development	Localization	Mucousmembrane involvementw	Description	Figure	Culprit drug(s)	Outcome
Moallem 2002[33] TEN	SLE/simultaneously	14/F	During the event ANA 1 : 5120, 5 months later ANA 1 : 10,240, thrombopenia, hypocomplementaemia, anaemia, later anti-dsDNA and lupus nephritis	None	5 months later malar rash after sun exposure	Fever, flaccid blisters/few days exfoliation > 40% BSA, Nikolsky positive, mechanical ventilation	Generalized	Blisters on palate, later keratopathy	Full-thickness epidermal necrosis	No	Amoxicillin/ clavulanic acid 1 week prior to the event	Discharged, methylprednisolone, IVIG, antibiotics
Samimi 2002[34] SJS	SLE/recent	9/F	Directly before the event elevated ESR, ANA 1 : 640, anti-DNA, anti-cardiolipin, decreased complement, lupus-nephritis, elevated liver function tests, cardiomegaly	Methylprednisolone 4 mg kg^{-1} daily for 6 days, followed by prednisone 60 mg daily, cyclophosphamide	Erythema on cheeks, eyelids, superficial oral erosions	Fever, diffuse blistering and desquamation, mechanical ventilation/ progressive few days	Face and trunk	Ocular, oral and vulvar mucositis	Numerous necrotic keratinocytes, interface changes, DIF negative	No	Azithromycin 2 weeks prior to event	4-day course IVIG 750 mg kg^{-1} daily, methylprednisolone 2 mg kg^{-1} daily; discharged 3 weeks later
Jongen-Lavrencic 2003[39] TEN	SLE/6 years	27/F	N.m., treated with hydroxychloroquine	No	N.m.	Fever, diffuse rash, diarrhoea, epidermal sloughing BSA 60%, mechanical ventilation, multiorgan failure	Diffuse, upper/ lower extremities	Desquamation lips	Skin necrosis with sloughing and subepidermal bullae consistent with TEN	No	Second dose of ciprofloxacin; 2 weeks before event 5-day course without reaction	Day 7 corticosteroids 65 mg daily, died day 28 due to severe acute respiratory distress syndrome and cardiac arrest

			Activity of LE			TEN/SJS-features			Histology			
Author/reported SJS/TEN	LE-type/ duration	Age (years) /sex	Laboratory/clinically	Immuno-suppres-sive drugs	LE-specific skin lesions	Lesions/time of deve-lopment	Localization	Mucous mem-brane involve-mentw	Description	Figure	Culprit drug(s)	Outcome
Matsushita 2006[35] SJS	SLE for 11 months	32/F	History of SLE for 11 months with lupus nephritis, antiphos-pholipid syndrome, arthritis, oral ulcers, facial oedema, pleu-risy, haematological and immunological disorders	Predni-solone 1 mg kg^{-1} daily; mizoribine 150 mg daily	Oral ulcer, facial oedema later facial erythema	Fever, facial erythema, small bullous erup-tions (< 5 mm) face and forearms/progression over 1 week	Face, forearm	Erosions of the oral cavity and eye mucosa	Some apoptotic keratinocytes (according to microphoto-graph in lower epidermis), inflammatory infiltrate with lymphocytes and neutro-phils (accord-ing to micro-photograph moderately dense, superfi-cial and deep)	OK	Mizoribine since 6 months, reintroduced after break 2 months earlier	Methylpredniso-lone 500 mg for 1 day followed by pred-nisolone 1 mg kg^{-1} daily, IVIG; symptoms disappeared within 1 month
Terrab 2006[36] SJS	SLE for 4 years	25/F	Stable SLE pre-existing, polyarthritis, lymphopenia, ANA 1 : 1280, anti-native DNA, decreased com-plement; simultane-ously with the event lupus nephritis, high antihistone, anaemia	Corticoste-roid 20 mg daily	Butterfly rash, pho-tosensitiv-ity, chronic discoid erythema-tosquamous atrophic plaques on ears, thighs; buccal ulcerations, necrotic pulpitis	Maculopapular purpuric exanthema, epider-molysis 10% of body surface/7 days after drug intake	Initially on the face with spreading over trunk and extremities	Discrete cheilitis, bilateral con-junctivitis	Subepidermal detachment with full-thick-ness epidermal necrosis (according to microphoto-graph mod-erately dense inflammatory infiltrates), DIF negative	Detail only	Terbinafine 7 days prior the event	Terbinafine stopped, cortico-steroids 1 mg kg^{-1} daily and bolus cyclophosphamide, favourable outcome after 15 days. 18 months later: decreased ANA, anti-DNA and antihistone nega-tive, normalization renal function, no new skin lesions

N.m., not mentioned; DIF, direct immunofluorescence; eos, eosinophils; BMZ, basal membrane zone; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibodies; ds-DNA, double-stranded DNA; BSA, body surface area; IVIG, intravenous immunoglobulins.

Cases of toxic epidermal necrolysis-like lupus erythematosus in the literature

Eight publications with 12 patients (comprising 13 episodes) were related to 'TEN-like LE' (**Table 5**).[17-24] Most patients experienced unusual subacute progression of LE over weeks or months, showing clinically 'TEN-like' features, but lacking an apparent trigger. TEN-like skin lesions did evolve from pre-existing annular or papulosquamous LE lesions, often accompanied by circulating Ro/SS-A autoantibody or minimal SLE activity. In some patients, however, TEN-like skin lesions rapidly evolved from a photodistributed confluent or patchy erythema otherwise characteristic for ACLE. Typically, such patients showed clear SLE activity with positive serological markers (antinuclear antibodies, anti-Ro/SS-A or rheumatoid factor).[19] Although clinically rather similar to SJS/TEN, the progression of 'TEN-like LE' developed rather slowly. Mucous membranes were most often not, or only focally, involved.

Table 5. List of reported cases of toxic epidermal necrolysis (TEN)-like lupus erythematosus (LE) in the literature

			Activity of LE			'TEN/SJS'-like features			Histology			
Author/ type of LE	LE type	Age (years) /sex	Laboratory/clinically	Immunosuppressive medication	LE-specific skin lesions	Lesions/time of development	Localization	Mucous membrane involvement	Description	Figure	Culprit drug(s)	Outcome
Bielsa 1987[17] SLE	SLE for 2 years	42/F	History of hypocomplementaemic urticarial vasculitis, neurological and renal LE; high fever, malaise; anti-Ro, proteinuria, decreased complement, previously ANA 1 : 1600, anti-DNA	Prednisolone 60 mg daily, cyclophosphamide 100 mg daily	Violaceous polycyclic erythematopapulosquamous, partly annular lesions with vesiculobullous edges on photoexposed skin areas	Progressive aggravation of previous lesions on to large blisters leaving denuded areas, Nikolsky positive	Abdomen, thighs, legs and feet Photo-distribution	Affected lips, but mucous membranes not involved	Necrotic epidermis, isolated necrotic keratinocytes in the adjacent epidermis with exocytosis of lymphocytes and neutrophils; superficial perivascular lymphocytic infiltrate; DIF: IgG, IgM, C3 at BMZ	Small high-power detail of the blister only	Doubtfully furosemide commenced 8 months before the event	Methylprednisolone 1 g for 3 days, remission obtained
Braverman 1998[18] *Four patients with SLE/SCLE*												
Patient 1	CLE for 9 years, SLE for 3 years	27/F	Pericarditis, lupus nephritis	Prednisolone, azathioprine	Bullae arising from urticarial plaques	Bullae arising from urticarial plaques/recurrent episodes	Denuded skin up to 40% BSA	N.m.	No detailed description, 'changes of erythema multiforme', DIF not performed	No	No	Repeatedly remissions after prednisone, death from sepsis and organ failure
Patient 2	SLE few months earlier	40/F	Anaemia, leucopenia, borderline thrombopenia, decreased complement, ANA 1 : 128 homogeneous, arthralgias, fever	N.m.	Diffuse nonscarring alopecia, periungual erythema	Fever, slowly spreading maculopapular rash, later bullae which broke/ recurrent over 3 months	Face, trunk, extremities	N.m.	No detailed description, 'changes of erythema multiforme/ TEN', DIF positive lupus band test	No	N.m.	Prompt resolution with prednisolone, recurrence when prednisolone was tapered
Patient 3	SCLE for 5 years	51/M	ANA 1 : 5125, anti-Ro, leucopenia, thrombopenia	N.m.	Generalized papulosquamous lesions	Vesicles, bullae and erosions within and at margins of papulosquamous lesions, peeling off in large sheets	Widespread	N.m.	No detailed description, 'changes of TEN,' DIF not performed	No	N.m.	Immediate healing with steroid therapy

Author/ type of LE	LE type	Age (years) /sex	Activity of LE: Laboratory/clinically	Activity of LE: Immunosuppressive medication	LE-specific skin lesions	'TEN/SJS'-like features: Lesions/time of development	'TEN/SJS'-like features: Localization	'TEN/SJS'-like features: Mucous membrane involvement	Histology: Description	Histology: Figure	Culprit drug(s)	Outcome
Patient 4	SLE for 2 years	35/F	Lupus nephritis, cerebritis	N.m.	N.m.	Maculopapular eruption evolving into TEN/over 6–8weeks	N.m.	N.m.	No detailed description, 'corresponding to TEN'	No	No	Successfully treated with prednisolone; however recurrence after 2 years
Mandelcorn 2003[19]												
Patient 1, First episode SLE	SLE for 9 years	42/F	Arthritis, serositis, malar rash, restrictive lung disease, no flare in the 12 months before presentation, at presentation ANA 1 : 2560 homogeneous, anti-Ro and anti-La, anti-DNA 1 : 1280, RF	Prednisone 5 mg daily	Acral violaceous macules and patches on the distal extremities suggestive of chilblains	Afebrile, systemically well, gradual developing painful annular, targetoid, red to violaceous plaques, some ulcerated with haemorrhagic crusts/gradual over 7 weeks	Widespread	Multiple erosions on buccal mucosa and tongue	Scattered necrotic keratinocytes in basal layer and epidermis with focal vacuolar changes, sparse upper dermal lymphocytic infiltrate, DIF negative	No	No	Prednisone 1·5 mg kg^{-1} dally tapered over 2 months with gradual resolution of symptoms
Patient 1, Second episode (3 months later) SLE						Afebrile, systemically well, erythema and painful erosions, partly encrusted, involving more than 70% BSA; Nikolsky sign positive/ gradual over 8 weeks	Extensive distribution on face, trunk, extremities	Erosions oral mucosa	Complete epithelial necrosis, sparse lymphocytic infiltrate in upper dermis, large numbers of bacterial colonies in the necrotic epithelium, indicative of secondary impetiginization, DIF negative	No	No	IVIG 1 g kg^{-1} daily for 3 days, prompt and complete resolution in 2 weeks, without recurrence
Patient 2 SCLE	No prior history of LE	76/F	ANA 1 : 320 speckled (1 : 160 homogeneous), -Ro, anti-La, RF; during previous 4 years 3 episodes of mild generalized annular bullous eruptions with oral ulcers	No	N.m.	Afebrile, systemically well, painful erythema, bullae, and erosions > 80% BSA, Nikolsky sign positive/progressive over 3 weeks	Face, trunk, and extremities	Oral and genital ulceration	Complete necrosis of epidermis, separation of necrotic epithelium, and extremely sparse lymphocytic infiltrate in papillary dermis, DIF negative	No	No new medication within 3 months before onset of the eruption	Prednisone 100 mg daily 5 days no improvement, followed by IVIG 1 g kg^{-1} daily for 3 days, skin lesions resolved over 3 weeks, without recurrence

Author/ type of LE	LE type	Age (years) /sex	Activity of LE		LE-specific skin lesions	'TEN/SJS'-like features		Mucous membrane involvement	Histology		Culprit drug(s)	Outcome
			Laboratory/clinically	Immunosuppressive medication		Lesions/time of development	Localization		Description	Figure		
Perera 2004[20] *Bullous* SCLE	No prior history of LE	59/F	History of autoimmune diseases (Graves disease, pernicious anaemia, alopecia areata), anti-Ro, HLA DR3	No	Recently blistering skin eruption in a photoaggravated distribution during sunny holiday	Afebrile, recurrent erythematous to papulosquamous lesions coalescing and denuding in sheets, in other areas intact and disrupted bullae, lesions confined to skin not covered by bathing costume	Extensive lesions on trunk and extremities, photodistribution, palms, soles unaffected	No	Initial biopsy: predominance of vacuolar degeneration at BMZ, sparse apoptotic keratinocytes; at admission: subepidermal blister, necrosis of the epidermis, basal layer vacuolization, apoptotic keratinocytes throughout all levels of the epidermis, DIF negative	Superficial detail	Vitamin B_{12} 3-monthly, thyroid hormone replacement in Graves disease	Initially given systemic steroids discontinued, topical clobetasol; cleared for 2 months, spontaneous recurrence with blistering on erythema, distribution typical for SCLE
Mutasim 2003[21] SCLE	No prior history of LE	31/F	Recently chills, leucopenia, ANA 1 : 160 speckled, anti-Ro, anti-La, photorelated lesions	No	Progressive deeply erythematous confluent patches with brownish desquamation over 1 year	Erythroderma with bullae	Large bullae on feet, photorelated flare 6 weeks after clearance	No	3 biopsies: focal to diffuse parakeratosis, mild to severe dyskeratosis of keratinocytes, focal full-thickness epidermal necrosis, mild to minimal superficial lymphocytic infiltrate, DIF positive	OK	Doubtfully, chlordiazepoxide HCL/ duration n.m.	Prednisone 1 mg kg^{-1} daily for 2 weeks than tapered, complete clearance in 4–5 weeks, generalized photorelated flare 6 weeks after discontinuation successfully treated with hydroxychloroquine, altogether eruption continued for several months after discontinuation of the drug

Author/ type of LE	LE type	Age (years) /sex	Activity of LE: Laboratory/clinically	Activity of LE: Immunosuppressive medication	LE-specific skin lesions	'TEN/SJS'-like features: Lesions/time of development	'TEN/SJS'-like features: Localization	Mucous membrane involvement	Histology: Description	Histology: Figure	Culprit drug(s)	Outcome
Ting 2004[22] SLE	No prior history of LE	53/F	ANA 1 : 640–1 : 1080 nucleolar, anti-dsDNA, anti-Ro, borderline anticardiolipin; elevated liver function tests with active lobular inflammation with cholestasis; after discharge deep venous thrombosis	No	No	Afebrile, acute onset, dusky, partly patchy erythema with numerous intact, but also denuded bullae, associated with positive Nikolsky sign	Face, neck, trunk and extremities, photodistribution (tanning bed), palms and soles uninvolved	Small erosion of the tongue	Biopsy blister edge: subepidermal blistering with full-thickness epidermal necrosis, adjacent epidermis with marked basal layer necrosis with satellite cell necrosis, mild lymphohistiocytic infiltrate at the DEJ and superficial and deeper perivascular infiltrates; DIF granular C3, fibrinogen at BMZ, perivascular granular C3, IgM, IgG	OK	Naproxen since 6 months, rabeprazole intermittently	IVIG 0·75 g kg^{-1} daily for 7 days, methylprednisolone 40 mg 2 x daily followed by prednisone tapered over 3 months; complete re-epithelialization; symptom free with hydroxychloroquine
Paradela 2007[23] ACLE	ACLE likely for 1·5 years	72/F	Leuco- and lymphopenia, anaemia, decreased C3 and C4, ANA 1 : 320 nucleolar, positive ENA and antiribosomal antibody, elevated liver function tests	Prednisone 15 mg daily	During the previous 1·5 years 2 episodes of erythematous papular eruption on upper trunk. Later discoid LE lesions	No fever or systemic symptoms, painful generalized slightly squamous erythema, bullae, erosions with haemorrhagic crusts; Nikolsky negative; palms and soles uninvolved	Face neck, trunk and extremities, involving > 70% BSA	No, in the course one ulcer on the hard palate	Hyperkeratosis (from microphotograph), atrophic epidermis, necrotic keratinocytes in the basal layer, focal full-thickness necrosis, focal subepidermal blistering, sparse superficial and deep perivascular and periadnexal lymphohistiocytic infiltrate, mild dermal mucin; DIF: granular IgM, IgG, C3 at BMZ	OK	Doubtfully, gabapentin	Methylprednisolone 20 mg for 3 days, followed by prednisone 1 mg kg^{-1} daily tapered over 2 weeks, discharged with 15 mg and complete healing of eroded lesions within 3 weeks 1 year later discoid LE

Author/ type of LE	LE type	Age (years) /sex	Activity of LE		LE-specific skin lesions	'TEN/SJS'-like features		Mucous membrane involvement	Histology		Culprit drug(s)	Outcome
			Laboratory/clinically	Immunosuppressive medication		Lesions/time of development	Localization		Description	Figure		
Simsek 2008[24] SLE	SLE for 7 years	28/F	Polyarthritis, pleurisy, photosensitivity, ANA, anti-dsDNA; leucopenia, anti-DNA 1 : 1080, anti-dsDNA 140 IU mL^{-1}	Prednisolone 5 mg daily	Subacute presentation over weeks with widespread erythema, multiple bullae	Afebrile, systemically well; 3 weeks history of widespread erythema, gradually becoming bullous and generalized and detachment 70% BSA, unaffected palms, soles	Erythema face, arms, upper chest, gradually generalized	No mucosal involvement	Full-thickness epidermal necrosis, separation epithelium and sparse lymphocytic infiltrate upper dermis; DIF granular IgG, faint IgA and C3 at BMZ	No	No	At admission i.v. methylprednisolone 1000 mg daily 3 days followed by increasing prednisolone to 80 mg daily and simultaneously IVIG 25 g daily 5 days without improvement and progression to > 90% BSA at day 15 and start plasmapheresis twice a week 5 sessions with prednisolone; at 3 weeks marked decrease detachment; after 5 weeks in hospital almost cleared; symptom free at 18 months on her earlier LE medication

ANA, antinuclear antibodies; ACLE, acute cutaneous LE; BMZ, basal membrane zone; BSA, body surface area; DEJ, dermoepidermal junction; DIF, direct immunofluorescence; dsDNA, double-stranded DNA; ENA, extractable nuclear antigen; IVIG, intravenous immunoglobulin; N.m., not mentioned; RF, rheumatoid factor; SLE, systemic LE.

Discussion

Patients with LE and extensive, partly bullous or erosive exanthema can be misinterpreted as SJS or TEN. Differentiation between SJS/TEN in patients with LE and TEN-like LE is sometimes complicated and relies on thorough analysis of complete clinical and histopathological data.

Unfortunately, most blistering skin lesions seen in the context of LE have been lumped into the broad designation of 'bullous LE'. However, a clear differentiation must be made between 'bullous SLE' in the strict sense, developing as a result of subepidermal blistering with neutrophilic infiltrate, clinically characterized by blisters being tense and raised, and bullous lesions in LE as a result of dramatic extension of the interface dermatitis.[9] Usually, LE-specific vesiculobullous skin lesions in LE develop as a result of the latter. Marked necrosis of keratinocytes of the (supra)basal layer and vaculoar degeneration lead to subepidermal blistering and almost full-thickness epidermal necrosis. Blisters can appear on active borders of annular lesions in SCLE or on chronic discoid LE lesions and can also develop in ACLE in patients with SLE.[22] Mandelcorn and Shear reported two patients with LE-associated TEN with features different from classic TEN and speculated about a novel manifestation.[19] However, it remains unclear whether or not such cases are indeed related to TEN or represent 'TEN-like LE'. Also, drug-induced SJS with 'concomitant aggravation of LE' has been reported.[36] Moreover, several case reports and small case series suggested that (S)LE is a risk factor for developing SJS/TEN.[40-42] In the international case–control study on SCAR as well as in the later EuroSCAR study, the frequency of so-called collagen vascular disease including SLE, rheumatoid arthritis, scleroderma, etc. was much higher in patients with SJS/TEN than in those with EEMM and control subjects. However, to date, (S)LE could not be identified as a risk factor by itself.

One special clinical expression of vesiculobullous LE was described by Rowell *et al.* in 1963.[43] They first described an erythema multiforme-like cutaneous eruption in LE in the setting of positive (speckled) antinuclear antibodies, anti-La/SS-B antibodies and rheumatoid factor without identifiable precipitating cause.[43] Progression to TEN has not been noted.[19] However, more recently published cases also reported TEN-like features.[44,45] Braverman suggested Rowell's syndrome as a limited form of 'TEN-like' ACLE or SCLE, both entities sharing the same pathogenic process.[18]

Furthermore, drug-induced LE more frequently is bullous.[46,47] Time latency between initiation of a drug and onset of LE ranges from 4 to 20 weeks.[46] Systemic manifestations are usually lacking. Data in the literature concerning the presence of antihistone antibodies are controversial and several authors do not consider them to be serological markers of drug-induced SCLE, although they are present in up to 95% of drug-induced SLE cases.[46,48] Most patients experience improvement or resolution of skin lesions within 8 weeks and decrease of titres of anti-Ro/SS-A, if present, within 8 months after discontinuation of drug treatment.[46]

SCLE and ACLE, in particular, may share clinical features of SJS/TEN. Generalized ACLE may present with morbilliform or maculopapular exanthema, spreading symmetrically, often also involving the palms and soles and the back of the hands and extensor surfaces of the fingers. Bullous lesions with epidermal detachment and painful mucosal erosions and ulcerations affecting the mouth (mostly focally on the hard palate, but also buccal mucosa, gingiva and uvula), nose, pharynx and vagina as well as the orificium urethrae may develop. The lips may present as erosive, crusty cheilitis.[49] Generally, about 20% of patients with LE have a history of oral ulcers at the onset of disease.[50,51] However, oral ulcers are rare and mostly focal.[22,51]

This study in a nation-wide registry allows detailed analysis of clinical and histopathological features of validated cases of SJS/TEN with a history of (S)LE. Contributing to the reliability of the diagnosis of SJS/TEN are the prospective and structured inclusion, data collection and validation, independent of outcome, exposure to medication or other risk factors. On the other hand, the nature of our study introduces the risk of underscoring the incidence of SJS/TEN in patients with a history of (S)LE. Retrospective retrieval of additional data on (S)LE and histological material implicates less complete information, resulting in insufficient substantiation of (S)LE, and/or unobtainable/irrelevant histological material, leading to exclusion of potential cases. Moreover, potential cases may have been missed when SJS/TEN was not suspected but lesions were directly ascribed to (S)LE by the treating physician.

In all cases, clinical and histopathological diagnostic criteria for SJS/TEN were in principle fulfilled. Although all patients also had a history of (S)LE, diagnosis of SJS/TEN was straightforward in nine of the 17 cases. These cases did not feature typical LE morphology, distinct photodistribution, LE flare shortly before the event or four or more histopathological features of LE. Furthermore, all had evident mucosal erosions, which in seven patients were not restricted to the lips and/or mouth.

In the other eight patients, sex, age (average age 47 years, range 30–78), mortality rate (37%), immunosuppressive therapy before the event (75%), median time between the index-day and the date of maximum blisters and erosions (8·5 days, range 4–12), and drug causality did not significantly differ from the total group of validated registry cases. However, several features did interfere with a straightforward diagnosis of SJS/TEN. Histopathological LE features (case 5), a preceding LE exacerbation (cases 9 and 15) or a combination of both (case 17) were interfering in four cases, while in the remaining four (cases 4, 6, 11 and 13) both clinical and histopathological LE features were found. Three of these (cases 4, 6 and 13) had exanthematic, often widespread LE-suspicious skin lesions weeks to months prior to the event. Mucous membrane involvement was absent in two (cases 11 and 13), compared with presence in all other patients. Evident photodistribution was recognized in cases 6, 9, 11 and 13. Positive anti-Ro or anti-La antibodies were mentioned in five of the eight cases, but only in one of the remaining nine patients.

Based on knowledge of the complete data, including medication and other risk factors, additionally supplied information on history of (S)LE and histopathological refinements, diagnosis in four cases was re-evaluated as SJS with concomitant histological features of LE

(case 5), SJS/TEN-overlap and EEMM/SJS, respectively, with an exacerbation of LE 1 month before the event (cases 15 and 9), and SJS/TEN-overlap with a relapse of cutaneous features of SLE 2 months before the event and concomitant histological features of LE (case 17). In four patients, a bullous manifestation of LE with a SJS/TEN-like appearance was more likely: 'SJS/TEN-like' SCLE/SLE (case 4), 'SJS/TEN-like' SLE (case 6) and 'SJS-like' (S)CLE and SLE (cases 11 and 13, respectively) (**Fig. 3a–c**; case 11).

In a retrospective analysis of SLE in 500 children, the prevalence of SJS was 1·2%.[40] However, criteria used for diagnosing SJS do not correspond to the criteria accepted nowadays and it is likely that the prevalence was considerably overestimated due to EEMM considered as SJS, especially in children.[40,42]

The frequency of (S)LE in the registry on SJS/TEN was 17 out of 1362 (substantiated) and 27 of 1362 (potentially), taking into account the excluded cases due to insufficient information on (S)LE, inappropriate histological material, and re-evaluation of SJS/TEN cases (1·2–2%).

The spectrum of drugs inducing SJS/TEN and LE is different.[46,52,53] Drugs highly suspected of causing SJS/TEN (allopurinol, three cases, and co-trimoxazole, two cases) were proportionally more often present in cases re-evaluated as SJS/TEN than in 'TEN-like' (S)LE.[40–42] Whether or not SLE is an independent risk factor for SJS/TEN is a matter of debate. The proportional over-representation in our study might also be due to co-dependent risk factors such as use of immunosuppressive drugs, or other shared risk factors such as genetic make-up resulting in a possible shared mechanism of acute diffuse epidermal apoptosis with associated production of inflammatory cytokines. From the results of the EuroSCAR study, it could not be concluded whether or not corticosteroids are a direct cause of SJS/TEN, a risk factor because of modifying the immune response, or a confounder.[52] Striking in that study was the fact that the multivariate relative risk for corticosteroids was restricted to the first 8 weeks of use, while the patients in this study were generally on long-term use. Although numbers are too small for statistically significant conclusions, the interval between the index-day and the date of maximum extent

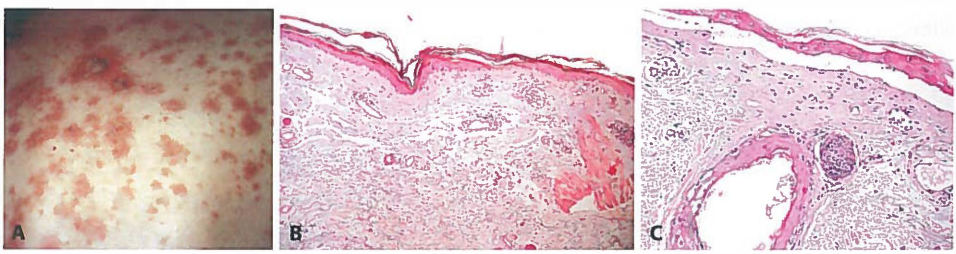

Figure 3. Case 11. A female patient with Stevens–Johnson syndrome-like cutaneous lupus erythematosus. (A) Erythematous erosive papules and plaques on the trunk. (B) Atrophic epidermis with compact hyperkeratosis. Scant vacuolar alteration at the dermoepidermal junction (DEJ) together with solitary necrotic keratinocytes mostly at lower levels [haematoxylin and eosin (H&E); original magnification × 100]. (C) Complete epidermal necrosis, vacuolar alteration at the DEJ of a sebaceous gland with solitary necrotic keratinocytes (H&E; original magnification × 200).

of detachment was generally slightly shorter in SJS/TEN cases compared with TEN-like LE. As illustrated by our study, the generally accepted qualification 'TEN-like' does not only concern cases mimicking TEN, but also the less severe variants-SJS and SJS/TEN-overlap.

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The spectrum of histopathological features in acute generalised exanthematous pustulosis: a study of 102 cases.

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Summary

Background: Acute generalized exanthematous pustulosis (AGEP) is a rare severe pustular reaction pattern with a typical clinical picture.

Objectives: To characterize the histopathological features of AGEP in a large series of cases with a validated diagnosis.

Methods: A multinational retrospective histopathological study was conducted. It included 102 hospitalized patients (recruited within the EuroSCAR and RegiSCAR studies) with a validated diagnosis of probable or definite AGEP. A systematic description of the histopathological features in AGEP was done based on a standardized grading system.

Results: Sub/intracorneal pustules (41%), intraepidermal pustules (20%) or combinations of them (38%) were observed in 102 cases. The pustules were usually large (> 15 keratinocytes) (82% and 89%, respectively) and regularly contained eosinophils (36% and 32%, respectively). Spongiform features were less prominent in the sub/intracorneal pustules compared with the intraepidermal pustules (44% and 95%, respectively). The main epidermal features were necrotic keratinocytes (67%), including incidental segmental necrosis (7%), and spongiosis (80%) with neutrophil exocytosis (77%). The main dermal features were papillary oedema (88%) and mixed superficial (100%), interstitial (93%), and mid/deep-dermal infiltrates (95%) containing neutrophils (100%) and eosinophils (81%). Follicular pustules were also seen (23%), but vasculitis generally was absent. Classical features of plaque-type psoriasis were infrequent and usually mild. No significant differences were observed between a subgroup of 16 cases with and 86 cases without psoriasis.

Conclusions: The present histopathological study concerns a large series of cases with a validated diagnosis of AGEP. It provides diagnostic clues in favour of AGEP in patients with a pustular eruption.

Introduction

Acute generalized exanthematous pustulosis (AGEP) is a rare, severe, acute-onset pustular reaction pattern characterized by a typical clinical picture and course. AGEP is attributed mostly to drugs, although other aetiologies such as viral infections due to human parvovirus B19, cytomegalovirus and Coxsackie B4, hypersensitivity to mercury and spider bite have been implicated.[1-12]

Clinically, AGEP is characterized by the sudden appearance of dozens of sterile, nonfollicular pinhead-sized pustules arising on oedematous erythema with a predilection of the big folds, or widespread distribution. Mild, nonerosive mucous membrane involvement (mostly oral) may occur in about 20% of cases. Other skin symptoms, such as marked oedema of the face, purpura, 'atypical target-like lesions' and blisters have been described but are not typical for AGEP. The course of AGEP is characterized in most cases by fever (≥ 38 °C) and elevated blood neutrophil count (≥ 7·0 × 10^9 L^{-1}). Mild eosinophilia may be present in about one-third of patients.[13] Pustules resolve spontaneously within a few days, followed typically by postpustular, pin-point desquamation. The reaction resolves fully in ≤15 days. Internal organs are generally not involved and the disease has a favourable prognosis, although secondary infection might pose a danger to patients in poor general medical condition. The reported mortality is 5%.[14]

Eruptions similar to AGEP have been described in the literature as toxic pustuloderma or pustular drug eruption,[15-21] or have been interpreted as special variants of other pustular diseases, such as exanthematic pustular psoriasis (PP), suspected to be triggered by drugs or infections.[22-23]

Knowledge of the histopathology of AGEP is based primarily on case reports and a few clinical studies.[1,3,4,13,24-29] The aim of the present study was to characterize the histopathological features in a large series of cases with a validated diagnosis of AGEP.

Patients and methods

Source of patients

The patients with AGEP came from two multinational studies devoted to Severe Cutaneous Adverse Reactions (SCAR): The EuroSCAR study, conducted in France, Germany, Italy, the Netherlands, Austria, Spain and Israel during the years 1997–2001[2,30] and the RegiSCAR study, conducted in France, Germany, Italy, the Netherlands, Austria and Israel since 2003.[31,32] In both studies AGEP cases were actively detected in a network of hospitals in Europe and Israel. Potential AGEP cases were patients admitted to hospital due to acute pustular skin reactions (i.e. community cases) or who developed such reactions during a hospital stay (i.e. hospital cases). They had dozens of pustules that could not be attributed to another definitive diagnosis. All

patients gave written informed consent to participate in these studies. The study was approved by the Helsinki Committee of each participating centre that recruited patients.

Case validation

An international committee of experts validated the diagnosis of AGEP based on a special standardized scoring system that was developed in the EuroSCAR study, the AGEP validation score.[2,33] Based on the score, patients were either excluded from the study or classified as definite, probable or possible cases.

Inclusion of cases

The present study population comprised patients with a definite or probable diagnosis of AGEP and a skin biopsy with slides available for histopathological investigation.

Histopathological evaluation

The histopathological study was performed on haematoxylin and eosin-stained sections. All four readers viewed the same slide with a multiheaded microscope and discussed it together at that time. When several sections were available for a particular patient only the most informative specimen was chosen, based on the proper representation of the epidermis and dermis and the presence of an acute inflammatory process, preferentially including a pustule. When several pustules were present in a section, the largest was evaluated.

Evaluation was based on a standardized list of histopathological parameters used for the diagnosis of AGEP. A severity scale of the various histopathological parameters, ranging from 0 to 3, was developed (**Table 1**), and the degree of severity was determined by consensus.

Analysis and statistics

Data were analysed using SPSS version 12 (SPSS, Chicago, IL, U.S.A.). The frequencies of different variables in two subgroups (with and without a background of psoriasis) were compared using the *t*-test for continuous variables, or the χ^2 or Fisher's exact test for differences in proportions, as appropriate.

Table 1. Histopathological parameters used in the evaluation of acute generalized exanthematous pustulosis

Histological parameter	Degree of severity
Pustule size[a]	
Small (< 10 keratinocytes)	1
Medium (10–15 keratinocytes)	2
Large (> 15 keratinocytes)	3
Spongiform pustule[b]	
Mild	1
Moderate	2
Prominent	3
Follicular pustule	
Accessory[c]	1
Predominant	2
Solitary[d]	3
Spongiosis	
Mild	1
Prominent	2
Vesicles	3
Exocytosis of neutrophils	
A few	1
Scattered	2
Many	3
Necrotic keratinocytes	
1 or 2	1
> 2	2
Segmental necrosis or more	3
Papillary oedema	
Discrete	1
Moderate	2
Severe	3
Infiltrates: superficial, interstitial, mid/deep-dermal	
Discrete	1
Moderate	2
Dense	3
Dermal neutrophils	
A few	1
Scattered	2
Full fields	3

Histological parameter	Degree of severity
Eosinophils (pustule or dermis)/erythrocyte extravasation	
1 or 2 cells	1
> 2 cells	2
Many cells	3
Munro abscesses	
1	1
2	2
> 2	3
Hyperkeratosis	
Mild	1
Moderate	2
Prominent	3
Granular cell layer/parakeratosis[e]	
Absent	0
Up to 1/3 the length of the biopsy	1
Up to 2/3 the length of the biopsy	2
Almost total	3
Suprapapillary plate thinning[f]	
1 papilla	1
2 papillae	2
> 2 papillae	3
Tortuous and dilated blood vessels/vasculitis[g]	
1 vessel	1
2 vessels	2
> 2 vessels	3
Rete ridges elongation/clubbing/fusion	
1	1
2	2
> 2	3
Mitosis	
Number per high power field (×40 magnification)	

[a]In cases with several pustules, the largest is used. [b]Accumulation of microaggregates of neutrophils separated by degenerated and thinned keratinocytes. [c]In conjunction with other types of pustules only. [d]Without other types of pustules. [e]Parakeratosis/granular layer above a pustule is not included. [f]Suprapapillary plate thinning of the epidermis is defined as fewer than three layers of keratinocytes above the papillae. [g]Leucocytoclastic vasculitis.

Results

The present study included 102 cases with a definite or probable diagnosis of AGEP: 86 of 134 cases from the EuroSCAR study and 16 of 70 cases from phase I of the RegiSCAR study (cases enrolled in the study until the end of 2004). Seventy cases (69%) originated from France, 22 (22%) from Israel (see Ref. 5 for the clinical profile of nine cases), and 10 (10%) from the Netherlands. A personal history of psoriasis was recorded in 16 cases (16%) (11 from the EuroSCAR study and five from the RegiSCAR study).

The skin biopsies were taken from a known clinical lesion in only 45 of the 102 cases (44%): 40 biopsies (39%) were obtained from pustules (sometimes associated with erythema, oedema or purpura) and five (5%) from nonpustular clinical lesions, described as erythema or oedema.

The prevalence rates of the broad range of histopathological parameters seen in the 102 cases are presented in **Table 2**. Pustules were found in 94 cases (92%) and the location of the pustules was sub/intracorneal in 41%, intraepidermal in 20%, and combined in 38%. In addition to subcorneal pustules, subcorneal pustules contiguous with intracorneal pustules, and intracorneal pustules were also seen. The intraepidermal pustules were located in the upper part of the epidermis, most often contiguous with subcorneal or sub/intracorneal pustules. The sub/intracorneal and intraepidermal pustules were usually large (>15 keratinocytes) in 82% and 89%, respectively, and regularly contained eosinophils (36% and 32%, respectively). Spongiform features were less prominent in the sub/intracorneal pustules compared with the intraepidermal pustules (44% and 95%, respectively). Follicular pustules were seen in 22 cases (23%). They were accessory, predominant, or alone. The main epidermal features (**Fig. 1–3**) were necrotic keratinocytes (67%) including segmental necrosis (7%), and spongiosis (80%) with neutrophil exocytosis (77%). The main dermal features were papillary oedema (88%), mixed superficial (100%), interstitial (93%), and mid/deep-dermal infiltrates (95%) containing neutrophils (100%)

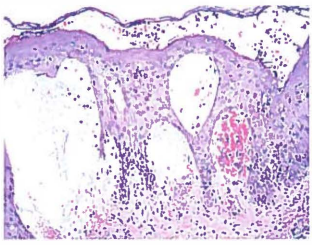

Figure 1. Large nonspongiform subcorneal pustule, papillary oedema, and erythrocyte extravasation (H&E, original magnification 20x10).

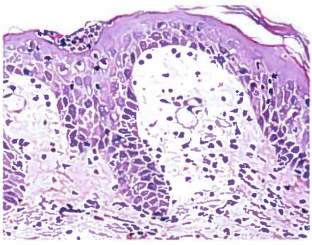

Figure 2. Small subcorneal pustule, presence of neutrophils and eosinophils in the epidermis and in the superficial dermis (H&E, original magnification 40x10).

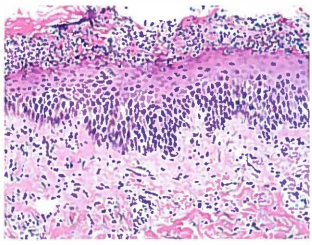

Figure 3. Large spongiform intraepidermal pustule with necrotic keratinocytes and spongiosis in the lower part of the epidermis. In the dermis there is discrete leucocytoclasia, but no vasculitis (H&E, original magnification 20x10)

and eosinophils (81%). Erythrocyte extravasation (54%) was also observed, but vasculitis occurred only once (1%). Classical features of plaque-type psoriasis were infrequent and usually mild. These included the presence of Munro abscesses (17%), parakeratosis (62%), suprapapillary plate thinning (7%), tortuous and dilated blood vessels (16%), and absence of the granular layer (3%). The calculated mean mitosis was 0·95 per high-power field at magnification ×40.

Table 2. The prevalence of histopathological parameters in 102 patients with acute generalized exanthematous pustulosis

Histopathological parameter	Degree of severity	Prevalence (%)
Pustules		
Sub/intracorneal and intraepidermal pustules		94 (92)
Sub/intracorneal pustules		39 (41)
Large	3	32 (82)
Small	1	4 (10)
Spongiform	1, 2, 3	17 (44)
Presence of eosinophils	1, 2, 3	14 (36)
Intraepidermal pustules		19 (20)
Large	3	17 (89)
Small	1	2 (10)
Spongiform	1, 2, 3	18 (95)
Presence of eosinophils	1, 2, 3	6 (32)
Combined (sub/intracorneal and intraepidermal)		36 (38)
Follicular pustules		22 (23)
Accessory (in conjunction with other pustules)	1	8 (36)
Predominant	2	9 (41)
Solitary	3	5 (23)
Epidermis		
Spongiosis		82 (80)
Mild	1	62 (76)
Exocytosis of neutrophils		79 (77)
A few	1	53 (67)
Necrotic keratinocytes		68 (67)
1–2 keratinocytes	1	32 (47)
> 2 keratinocytes	2	31 (46)
Segmental necrosis	3	5 (7)
Dermis		
Papillary oedema		90 (88)
Discrete	1	41 (45)
Moderate	2	24 (27)
Severe	3	25 (28)
Superficial infiltrates		102 (100)
Moderate	2	76 (74)
Mid/deep-dermal infiltrates		97 (95)
Discrete	1	64 (66)

Histopathological parameter	Degree of severity	Prevalence (%)
Interstitial infiltrates		95 (93)
Discrete	1	38 (40)
Moderate	2	36 (38)
Dermal neutrophils		102 (100)
A few	1	24 (23)
Scattered	2	60 (59)
Dermal eosinophils		83 (81)
A few	1	61 (73)
Vasculitis		1 (1)
Erythrocyte extravasation		55 (54)
1–2 cells	1	27 (49)
> 2 cells	2	26 (47)
Many	3	2 (4)
Classical plaque-type psoriatic changes		
Munro abscess		17 (17)
1	1	10 (59)
≥ 2	2, 3	7 (41)
Granular cell layer		99 (97)
None	0	3 (3)
Parakeratosis		63 (62)
Mild	1	35 (55)
Moderate	2	24 (38)
Hyperkeratosis		26 (25)
Mild	1	25 (96)
Suprapapillary plate thinning		7 (7)
Mild	1	7 (100)
Tortuous and dilated blood vessels		16 (16)
Mild	1	8 (50)
Moderate	2	8 (50)
Rete ridge elongation		78 (76)
Mild	1	38 (49)
Moderate	2	32 (41)
Rete ridge clubbing		52 (51)
Mild	1	39 (75)
Rete ridge fusion		83 (81)
Mild	1	35 (42)
Moderate	2	39 (47)
Mitosis		
Number per high-power field (×40 magnification)	Mean	0·95

Three levels of prevalence were observed. All AGEP cases showed superficial infiltrates (mostly moderate) and dermal neutrophils (mostly scattered). Additional features observed in 80–99% of AGEP cases were large sub/intracorneal or intraepidermal pustules, spongiform intraepidermal pustules, spongiosis (mostly mild), papillary oedema, mid/deep-dermal infiltrates (mostly discrete), interstitial infiltrates (mostly discrete to moderate), dermal eosinophils (usually just a few), absence of vasculitis, presence of granular cell layer, fusion of rete ridges (mild to moderate), and absence of classical features of plaque-type psoriasis (Munro abscesses, suprapapillary plate thinning, tortuous and dilated blood vessels, and a high mitotic rate). Additional features observed in 50–79% of AGEP cases were necrotic keratinocytes, parakeratosis, extravasation of erythrocytes, exocytosis of neutrophils (usually just a few), rete ridge elongation (mild to moderate), and clubbing (mostly mild).

There were no statistically significant differences in the prevalence of histopathological parameters between a subgroup of 16 AGEP cases (16%) with a personal history of psoriasis and the 86 AGEP cases with no personal history of psoriasis (data not shown).

Discussion

The present study, which focused on the histopathological evaluation of AGEP, included unique features in design and methodology: (i) the study population consisted of patients recruited in two multinational studies with a validated diagnosis of probable or definite AGEP; (ii) validation of the diagnosis was based on a special standardized scoring system, the AGEP validation score;[2,33] (iii) it included the largest series of AGEP cases; (iv) the histopathological evaluation of AGEP was based on direct investigation of the slides by four investigators using a multiheaded microscope; and (v) evaluation was based on a standardized grading system developed by the authors, related to pustules, epidermis, dermis, and psoriasis-like changes.

The main histopathological findings, in a previous clinical study of 63 cases of AGEP[13] with 64 biopsies from 48 patients reviewed by two investigators, were superficial spongiform pustules (66%), papillary oedema (61%), polymorphous perivascular infiltrate with eosinophils (34%), and leucocytoclastic vasculitis with fibrinoid deposits (20%). Focal necrosis of keratinocytes was observed in 25% and the epidermis was normal or spongiotic without psoriasiform hyperplasia in 61%.

In comparison, the present study of 102 AGEP cases disclosed several unique histopathological features: (i) sub/intracorneal pustules and intraepidermal pustules, often contiguous with sub/intracorneal pustules; (ii) pustules that showed a higher prevalence of spongiform features (95% of intraepidermal pustules); (iii) a higher prevalence of necrotic keratinocytes (67%), papillary oedema (88%) and dermal eosinophils (81%); (iv) a marked prevalence of interstitial and mid/deep-dermal infiltrates (93% and 95%, respectively) and of dermal neutrophils (100%), not emphasized previously; (v) psoriasiform hyperplasia (rete ridge elongation, clubbing and fusion

at rates of 76%, 51% and 81%, respectively) that was usually mild, although more common than previously reported. Munro abscesses, which are generally associated with psoriasis, were observed in 17% of cases; (vi) on the other hand, vasculitis, which was strictly defined by the presence of vascular fibrinoid alteration and leucocytoclasia, was observed in the present study only once, indicating that vasculitis is not a diagnostic feature of AGEP. As erythrocyte extravasation occurred in 54% of cases, the previously reported high rate of vasculitis in AGEP might be attributed to misinterpretation of leucocytoclasia and/or erythrocyte extravasation as vasculitis, or to a diagnostic confusion of AGEP with pustular vasculitis.[34] (vii) Histologically, follicular pustules were found in 23% of cases. Although the distribution of the pustular eruption in AGEP is mostly nonfollicular,[13] the occurrence of follicular pustules in association with nonfollicular pustules has been reported.[3,5] Thus, the presence of follicular pustules would appear not to exclude the diagnosis of AGEP.

Differences between the histopathological features of AGEP reported in various case reports and clinical studies might be attributed to case definition or different stages in the evolution of the skin lesions analysed. It was shown in a study of 21 AGEP cases[26] that the histopathological features vary in relation to the age of the skin lesion. Thus, biopsies of early lesions showed marked to moderate papillary dermal oedema and a mixed dermal inflammatory infiltrate, often with erythrocyte extravasation, and some leucocytoclasia. Biopsies of well-developed lesions showed spongiform pustules within the epidermis and occasional dyskeratotic cells with residual perivascular dermal oedema. Although no definitive vasculitis was seen, leucocytoclasia was observed within the dermal infiltrate in the majority of biopsy specimens obtained > 48 h after the onset of the eruption.

A wide spectrum of pustular reactions can easily be differentiated from AGEP both clinically and histologically (e.g. bacterial folliculitis, acne, dermatophyte infections, impetigo, infantile chronic acropustulosis, Sweet syndrome, IgA pemphigus, necrolytic migratory erythema, bowel bypass syndrome, Behçet disease and staphylococcal scalded skin syndrome). However, the differential diagnosis between AGEP and generalized PP, especially the acute von Zumbusch type, may be difficult clinically and histologically. Various histological features in PP bear similarity to AGEP, including superficial spongiform pustules, neutrophils beneath the stratum corneum, acanthosis and papillary oedema. On the other hand, characteristic for PP is the spongiform macropustule, arising from neutrophils that migrate from the dermal papillary capillaries into the epidermis, while dermal infiltrates are superficial and lymphocytic, usually lacking eosinophils. In addition, classical epidermal changes of psoriasis vulgaris vary and may be rather prominent in PP.[35,36]

Several histopathological features that were observed in the present study may point to the diagnosis of AGEP. These include superficial spongiform pustules, spongiosis, exocytosis of neutrophils, necrotic keratinocytes, papillary oedema, mixed dermal infiltrates, including mid/deep-dermal and interstitial infiltrates, containing neutrophils and eosinophils, and the paucity of classical plaque-type psoriatic changes (i.e. Munro abscesses, absence of granular layer,

suprapapillary plate thinning, tortuous and dilated blood vessels). The diagnosis of AGEP may be based on these key histopathological features combined with clinical signs in favour of AGEP including an abrupt onset, a short duration (≤ 15 days), association with recently introduced drugs, spontaneous resolution after withdrawal of the culprit drugs, and a nonrecurrent tendency.[2,6,13]

It has been reported that AGEP may occur in patients with psoriasis.[2,13] Accordingly, AGEP has been alleged to be a variant of PP, that could be triggered by a variety of exogenous factors such as drugs or infections.[13,22–25,37] In the present study a personal history of psoriasis was recorded in 16 (16%) of the 102 AGEP cases. No significant differences were observed between the subgroup of 16 AGEP cases with a personal history of psoriasis and the other 86 AGEP cases. Nevertheless, our study does not support the assumption that any acute pustular eruption occurring in patients with a psoriatic background is necessarily PP.

Several of the prevalent key features in favour of AGEP may imply its aetiopathogenesis:

1. The prominent presence of eosinophils in the skin of patients with AGEP, both within the pustules and in the dermis, is in agreement with the presence of blood eosinophilia observed in about a third of patients with AGEP.[13] The presence of tissue and blood eosinophilia, which is a hallmark of many drug-induced allergic reactions, suggests that AGEP is a hypersensitivity reaction, probably drug-induced.[38,39] Eosinophilia observed in AGEP may be attributed to the rare presence of interleukin (IL)-8/CXCL8-producing T-cell clones, which display a Th2-type cytokine profile with high IL-4 and IL-5 secretion.[40–42]

2. The presence of necrotic keratinocytes in AGEP has been reported in other drug eruptions including exanthematic drug eruptions and drug eruptions characterized primarily by interface dermatitis such as lichenoid drug eruptions, Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and fixed drug eruptions.[43] Although SJS and TEN are drug-induced reactions manifested by full-thickness epidermal necrosis and only a very sparse inflammatory infiltrate, some similarity may exist between AGEP and SJS or TEN.[27,44] The necrotic keratinocytes observed in AGEP can be induced by cytotoxic drug-specific T cells (CD8+ or CD4+).[45]

3. The neutrophilic inflammation observed in AGEP is unusual in allergic drug reactions. The prominent presence of dermal neutrophils in AGEP may reflect their recruitment by the potent neutrophil-attracting chemokine IL-8/CXCL8, secreted by drug-specific T cells (CD4+ and CD8+) and keratinocytes. Factors produced by the IL-8/CXCL8-producing T cells reduce neutrophil apoptosis, thus enhancing neutrophil survival and leading to the sterile pustular eruption found in AGEP.[39–42]

4. The mid/deep-dermal perivascular infiltrates and extravasation of erythrocytes which were observed in AGEP have been reported in other drug-induced eruptions, even in the absence of vasculitis, and may point to a drug aetiology.[38,46]

In conclusion, the present study, conducted in a large series of patients with AGEP with a validated diagnosis, disclosed a spectrum of histopathological features that provides additional

support for the concept that AGEP is a separate entity that can occur as an acute episode, even in patients with psoriasis.

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The histopathological spectrum of acute generalized exanthematous pustulosis (AGEP) and its differentiation from generalized pustular psoriasis.

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Abstract

Background: Acute generalized exanthematous pustulosis (AGEP) represents a severe, acute, pustular skin reaction that is most often induced by drugs. AGEP can be difficult to differentiate from generalized pustular psoriasis (GPP) both clinically and histopathologically. We present a systematic description of the histopathological spectrum of AGEP and GPP with a focus on discriminating features.

Materials and methods: A retrospective, descriptive, comparative histopathological study was completed utilizing step sections of 43 biopsies of 29 cases with a validated diagnosis of probable or definite AGEP and 24 biopsies of 19 cases with an established diagnosis of GPP.

Results: In AGEP, biopsies from erythema and pustules showed minor differences, whereas histopathology of the acute stage of GPP showed major differences compared to the chronic stage. Comparing AGEP and GPP, the presence of eosinophils, necrotic keratinocytes, a mixed interstitial and mid-dermal perivascular infiltrate and absence of tortuous or dilated blood vessels were in favor of AGEP. Moreover, chronic GPP was characterized by prominent epidermal psoriatic changes. The frequency of a psoriatic background of AGEP patients in our study was higher than that of psoriasis in the general population. However, histopathology of a subgroup of AGEP patients with a personal history of psoriasis revealed no significant differences from the other AGEP patients.

Conclusions: The spectrum of histopathological features of both AGEP and GPP is presented. Despite considerable overlap, subtle consistent histopathological differences and the grade of severity of specific features can help in differentiation. We could neither substantiate earlier reports that follicular pustules exclude AGEP nor did we see vasculitis as a specific feature in AGEP. Our study also supports the concept that AGEP is a separate entity that is distinct from GPP.

Introduction

In the past, most widespread sterile pustular eruptions were classified as generalized pustular psoriasis (GPP), a rare variant of psoriasis with several subtypes. The most severe and recalcitrant variant, the von Zumbusch type, is characterized by an acute generalized eruption of pustules on an erythematous base, sometimes lasting for weeks and often accompanied by fever and leukocytosis. Other types, such as annular pustular psoriasis, are subacute or even chronic and can either be widespread or localized. Psoriasis vulgaris may proceed, accompany or follow the pustular episode.[1-3]

In 1968, in a comprehensive review of 104 cases of GPP, Baker and Ryan[1] identified on clinical grounds five cases of exanthematous pustular psoriasis with short self-limiting courses which were presumably precipitated by infections and/or drugs. In 1980, Beylot et al.[4] termed this rare reaction type as acute generalized exanthematous pustulosis (AGEP). AGEP is mainly induced by drugs, but occasionally it can be precipitated by other causes such as viral infections.[5] Pustular rashes similar to AGEP have been described as toxic pustuloderma, pustular drug rash, (subcorneal) pustular drug eruption or drug-induced GPP.[6-10]

Clinically, AGEP is characterized by the sudden appearance of dozens of sterile, non-follicular, small pustules on edematous erythema with a widespread distribution or a predilection for the face and/or skin folds. Mild non-erosive mucosal involvement, mostly oral, may sometimes occur. Other skin signs such as facial edema, purpura, target-like lesions and blisters have been described but are not typical for AGEP. Fever, neutrophilia and mild peripheral blood eosinophilia (in a third of patients) are present. After elimination of the causative culprit, pustules associated with AGEP disappear in a few days, typically followed by postpustular desquamation, and the reaction fully resolves within 15 days. Usually, internal organs are not involved and overall prognosis is good, although lethal outcome has been reported.[11,12]

AGEP can be difficult to differentiate from GPP both clinically and histopathologically. Clinically, signs in favor of AGEP are abrupt onset, short duration, polymorphous lesions, association with recently started drugs and spontaneous healing after their elimination, non-recurrence and absence of arthritis or a personal or family history of psoriasis. Knowledge of the histopathology of both AGEP and GPP is based on case reports and small clinical studies.[4,13-22] Histopathological differentiation of AGEP from GPP has not been well documented and some even consider distinction based strictly on dermatopathology to be impossible.[23] The aim of the present study was to characterize the histopathological spectrum of AGEP and GPP and to find clues for differentiating these two disorders.

Materials and methods

Materials

We included 29 consecutive cases, evaluated as definite or probable AGEP, and 19 consecutive cases of GPP, that visited the Department of Dermatology of the University Medical Center Groningen between 1992 up until mid-2009 and for which biopsies of the active phase were available. All patients were seen in the active phase of the disease. Clinical information, charts, photographs, slides and information on the type and duration of the lesion from which the biopsy was taken were available. Diagnosis and grade of probability of AGEP (23 definite and 6 probable) were evaluated according to the validation system of Sidoroff et al.[11] Diagnosis of GPP was based on history, course, clinical charts and photographs.[1-3]

Biopsies were divided into subgroups: those for AGEP taken from erythema or a visible pustule, and those for GPP taken from acute pustules on erythematous, recently uninvolved skin representing acute GPP (aGPP), or from pustules on longer existing lesions, representing chronic GPP (cGPP). In each subgroup, only one biopsy of a case was randomly selected.

From the enrolled cases of AGEP, 43 biopsies (27 from visible pustules and 16 from erythema) and from GPP, 24 biopsies (14 from aGPP and 10 from cGPP) were studied.

Pathologic evaluation

The study was performed on step sections (regularly including additional step sections) of paraffin-embedded tissue, stained with hematoxylin and eosin. All processed slides were systematically evaluated according to parameters and grades listed in Table 1. Scoring was based on independent investigation by the first two authors, followed by a mutual meeting at a two-headed microscope where consensus was reached. The first author was the treating physician, not blinded for diagnosis, while the second author had no other information than the pending differential diagnosis.

Table 1. Scoring system of histopathological parameters used for evaluation of acute generalized exanthematous pustulosis and generalized pustular psoriasis

Parameter/severity score	0	1	2	3
Pustule size*	No	<10 Keratinocytes	10–15 Keratinocytes	16–30 Keratinocytes
Macro-pustule size	No	31–60 Keratinocytes	>60 Keratinocytes	—
Spongiform character pustule	No	Mild	Moderate	Severe
Munro(-like) abscesses	No	1	2	>2
Hair follicular pustule	No	Accessory†	Predominant	Solitary‡
Necrotic keratinocytes	No	1 or 2	3–10	>10
Neutrophilic exocytosis	No	Few	Scattered	Many
Spongiosis	No	Mild	Moderate	Vesicles
Papillary edema	No	Mild	Moderate	Severe
Infiltrates	No	Mild	Moderate	Dense
Eosinophils (pustule)	No	1 or 2	3–5	>5
Eosinophils (dermal)	No	1 or 2	3–10	>10
Neutrophils (dermal, papillary)	No	Few	Scattered	Full fields
Leukocytoclasia	No	Mild	Moderate	Severe
Vasculitis	No	1 Vessel	2 Vessels	>2 Vessels
Hyperkeratosis	No	Mild	Moderate	Severe
Parakeratosis	No	Mild	Moderate	Severe
Granular cell layer	Totally preserved	Mostly preserved	Severely diminished	Missing
Rete ridge changes (elongation, fusion and/or clubbing)	No	Mild	Moderate	Severe
Mitosis	No	<1.5/HPF	1.5–2.4/HPF	≥2.5/HPF
Suprapapillary plate thinning	No	1 Papilla	2 Papillae	>2 Papillae
Tortuous, dilated blood vessels	No	1 Capillary loop	2 Capillary loops	>2 Capillary loops

HPF, high power field at magnification 40× (0.25 mm^2).

*Pustule size: in case of several pustules, the largest is documented.

†Only in conjunction with other types of pustules (hair follicular pustule, accessory).

‡Without other types of pustules (hair follicular pustule, solitary).

Statistical analysis

We used the Fisher exact test for comparison of groups with respect to dichotomous variables. For comparison of groups with respect to severity scores, a linear trend test with exact calculated p values was used. A two-sided p value of 0.05 or less was considered as statistically significant. Data were analyzed using SPSS (version 16, SPSS, Chicago, IL).

Results

The gender–age distribution in AGEP was 12 male, 17 female, mean age 58.2 years (range 3–86), and in GPP 5 male, 14 female, mean age 55.6 years (range 0–80).

The detailed spectrum of the histopathological features in our study of 43 biopsies (27 from pustules and 16 from erythema) of AGEP is presented in **Table 2**. All biopsies showed at least one pustule. We observed intracorneal and subcorneal pustules, sometimes contiguous to intraepidermal or intracorneal, and combinations of these pustules in various sizes (**Fig. 1a,e**). Although often present at several levels, the accent of the pustules was generally subcorneal to subcorneal/intraepidermal. All pustules were neutrophil-rich with acantholytic epidermal cells and 58% also contained eosinophils (generally sparse). Most spongiform were the subcorneal/intraepidermal pustules (**Fig. 1c**). Although pustules were generally non-follicular, follicular pustules were observed as well (26%), most often accessory to other pustules, but incidentally also solitary. Munro(-like) abscesses (**Fig. 1e**) were noticed in 21% and macro-pustules in 40% of the biopsies (**Fig. 1a,b,d**).

Solitary necrotic keratinocytes (88%), most often discrete, neutrophilic exocytosis (91%) and spongiosis (100%) were common (**Fig. 1c,e**). Papillary edema (91%) was mostly discrete (**Fig. 1a,c,d**). Superficial and mid-dermal perivascular infiltrates, as well as interstitial infiltrates, were always present and of a mixed cellular type, generally also containing neutrophils (100%) and eosinophils (95%) (**Fig. 1a–e**). Often, mid-dermal infiltrates were also localized rather deep, lower than the upper third of the mid-dermis. The majority of cases showed erythrocyte extravasation and leukocytoclasia (**Fig. 1e**), but vasculitis, expressed by fibrinoid changes of the endothelial wall, was seen in only one patient.

Parakeratosis and rete ridge changes such as elongation, clubbing and fusion were regularly present, but often rather discrete. Other psoriasiform features such as hyperkeratosis, suprapapillary plate thinning and tortuous, dilated blood vessels were absent or only seen in a minority (**Fig. 1d**). The mitotic rate was generally under 1.5/high power field of 0.25 mm^2.

Histopathologically biopsies taken from erythema all revealed small pustules, mainly subcorneal to subcorneal/intraepidermal, whereas those from visible pustules were generally large with a more varied localization (**Fig. 1a–d**). Moreover, biopsies from pustules showed more pronounced rete ridge changes (**Fig. 1c,d**) and heavier infiltrates.

Comparison of 27 biopsies from pustules in AGEP with 14 biopsies of aGPP and 10 of cGPP showed several significant differences (**Table 3**). In GPP, pustules contained no eosinophils. Compared to AGEP, they generally contained more lysed keratinocytes and were more spongiform and were situated at a slightly higher epidermal level. Macro-pustules were prominent in GPP; in cGPP they were often situated at a more superficial epidermal level (**Fig. 2a**), while in aGPP they were often quite large (**Fig. 3a**). Psoriasiform epidermal changes were most prominent in cGPP

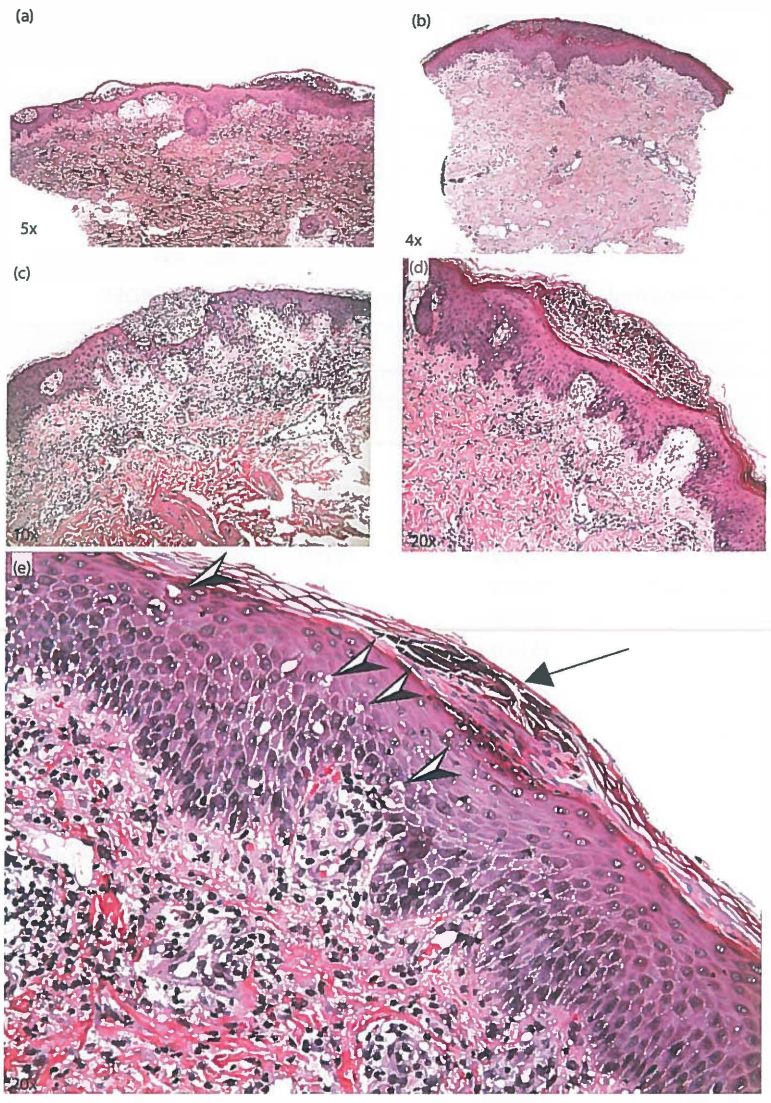

Figure 1. Histopathology of acute generalized exanthematous pustulosis. a) Spongiform pustules at various epidermal levels. b) Slightly spongiform subcorneal macro-pustule with a superficial and (lower) mid-dermal, perivascular and interstitial dermal infiltrate. c) Slightly spongiform subcorneal-intraepidermal pustule, minor acanthotic rete ridge changes, spongiosis, neutrophilic exocytosis, papillary edema and a mixed perivascular and interstitial infiltrate. d) Subcorneal macro-pustule, slightly acanthotic rete ridge changes, papillary edema, dilated papillary vessels, mixed perivascular and interstitial infiltrates. e) Small sub-/intracorneal pustule contiguous with a Munro-like abscess (arrow), spongiosis, few epidermal necrotic keratinocytes (arrowheads), erythrocyte extravasation, discrete leukocytoclasia and mixed perivascular and interstitial infiltrate including eosinophils. Hematoxylin and eosin, original magnification: (a) ×50, (b) ×40, (c) ×100 and (d,e) ×200.

(**Fig. 2a,b**). Most striking in GPP was the consistent presence of tortuous, dilated blood vessels (96%) (**Figs. 2a,b and 3b**). Compared with AGEP, necrotic keratinocytes and dermal eosinophils were significantly less present in GPP. The infiltrate in GPP was mainly superficial, perivascular, less pronounced and mainly mononuclear, while in AGEP the infiltrate was also deeper and interstitial. Neutrophils in aGPP were markedly located in the papillary dermis in comparison to AGEP and cGPP (**Fig. 3a–c**).

Table 2. Prevalence of histopathological features in pustules and erythema in AGEP

Histopathological parameters	Prevalence		
	AGEP total *n* = 43 (grade 2,3)	AGEP pustule *n* = 27 (grade 2,3)	AGEP erythema *n* = 16 (grade 2,3)
Pustules			
Munro(-like) abscesses	9 (5)	7 (4)	2 (1)
Intra-/subcorneal pustules	39 (24)	24 (18)	15 (6)
Spongiform	*31 (16)*	*18 (12)*	*13 (4)*
Subcorneal-intraepidermal pustules	26 (24)	18 (18)	8 (6)
Spongiform	*26 (18)*	*18 (15)*	*8 (3)*
Eosinophils in pustule	25 (10)	16 (9)	9 (1)
Macro-pustules	17 (12)	17 (12)	0 (0)
Hair follicular pustules	11	8	3
Epidermis			
Necrotic keratinocytes	38 (23)	22 (16)	16 (7)
Neutrophilic exocytosis	39 (20)	26 (16)	13 (4)
Spongiosis	43 (19)	27 (12)	16 (7)
Dermis			
Papillary edema	39 (17)	25 (12)	14 (5)
Superficial infiltrate	43 (37)	27 (25)	16 (12)
Interstitial infiltrate	43 (21)	27 (17)	16 (4)
Upper mid-dermal infiltrate	43 (33)	27 (23)	16 (10)
Lower mid-dermal infiltrate	30 (8)	18 (5)	12 (3)
Eosinophils	41 (32)	26 (21)	15 (11)
Neutrophils infiltrate	43 (32)	27 (22)	16 (10)
Neutrophils papillary	38 (14)	26 (13)	12 (1)
Leukocytoclasia	33 (11)	24 (7)	9 (4)
Psoriasiform (epidermal) changes			
Hyperkeratosis	7 (0)	5 (0)	2 (0)
Parakeratosis	16 (3)	12 (3)	4 (0)
Stratum granulosum	9 (1)	8 (1)	1 (0)
Rete ridge changes	20 (11)	16 (11)	4 (0)
Mitosis	43 (6)	27 (4)	16 (2)
Suprapapillary plate thinning	0 (0)	0 (0)	0 (0)
Tortuous, dilated blood vessels	7 (1)	6 (1)	1 (0)

AGEP, acute generalized exanthematous pustulosis.

Table 3. Comparison of histopathological features in pustular lesion in AGEP, aGPP and cGPP

	Prevalence			Significance (p value)	
Histopathological parameters	AGEP pustule $n = 27$ (grade 2,3)	aGPP $n = 14$ (grade 2,3)	cGPP $n = 10$ (grade 2,3)	AGEP aGPP	AGEP cGPP
Pustules					
Munro(-like) abscesses	7 (4)	1 (1)	8 (8)	NS	<0.01
Intra-/subcorneal pustules	24 (18)	14 (14)	10 (10)	<0.01	0.02
Spongiform	*18 (12)*	*14 (13)*	*10 (5)*	*<0.01*	*NS*
Subcorneal-intraepidermal pustules	18 (18)	8 (8)	3 (3)	NS	0.02
Spongiform	*18 (15)*	*8 (8)*	*3 (3)*	*NS*	*NS*
Eosinophils in pustule	16 (9)	0 (0)	0 (0)	<0.01	<0.01
Macro-pustules	17 (12)	14 (13)	10 (4)	<0.01	0.01
Hair follicular pustules	8	3	2	NS	NS
Epidermis					
Necrotic keratinocytes	22 (16)	2 (0)	1 (0)	<0.01	<0.01
Neutrophilic exocytosis	26 (16)	13 (11)	10 (6)	NS	NS
Spongiosis	27 (12)	14 (5)	9 (0)	NS	<0.01
Dermis					
Papillary edema	25 (12)	13 (4)	7 (1)	NS	NS
Superficial infiltrate	27 (25)	14 (7)	10 (4)	<0.01	<0.01
Interstitial infiltrate	27 (17)	9 (3)	3 (1)	<0.01	<0.01
Upper mid-dermal infiltrate	27 (23)	5 (0)	7 (2)	<0.01	<0.01
Lower mid-dermal infiltrate	18 (5)	3 (0)	0 (0)	0.01	<0.01
Eosinophils	26 (21)	1 (0)	2 (0)	<0.01	<0.01
Neutrophils infiltrate	27 (22)	14 (6)	8 (4)	0.04	0.02
Neutrophils papillary	26 (13)	14 (13)	8 (5)	<0.01	NS
Leukocytoclasia	24 (7)	7 (2)	2 (0)	0.03	<0.01
Psoriasiform (epidermal) changes					
Hyperkeratosis	5 (0)	4 (2)	10 (8)	NS	<0.01
Parakeratosis	12 (3)	4 (2)	9 (6)	NS	<0.01
Stratum granulosum	8 (1)	10 (3)	10 (7)	0.03	<0.01
Rete ridge changes	16 (11)	6 (4)	10 (9)	NS	0.02
Mitosis	27 (4)	14 (5)	10 (7)	0.05	<0.01
Suprapapillary plate thinning	0 (0)	1 (0)	5 (2)	NS	<0.01
Tortuous, dilated blood vessels	6 (1)	13 (12)	10 (10)	<0.01	<0.01

AGEP, acute generalized exanthematous pustulosis; aGPP, acute generalized pustular psoriasis; cGPP, chronic generalized pustular psoriasis; NS, non-significant.

Histopathology of a subgroup of seven AGEP patients with a personal history of psoriasis showed no significant differences with cases without pre-existing psoriasis. However, slight psoriasiform changes and presence of tortuous/dilated blood vessels were seen more often in this subgroup (**Fig. 1d**).

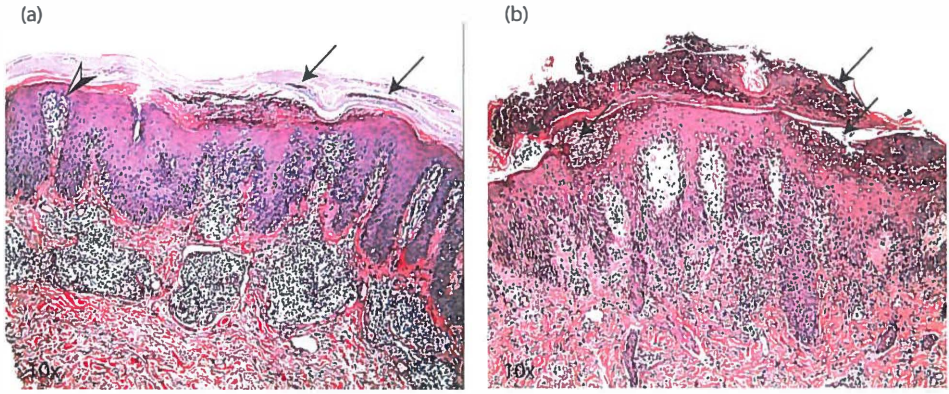

Figure 2. Histopathology of chronic generalized pustular psoriasis (cGPP). a) Club-shaped psoriatic rete ridges with hyperkeratosis, parakeratosis, Munro abscesses (arrows), epidermal plate thinning and sub-/intracorneal pustule with dilated, tortuous vessels (arrowhead) and superficial perivascular mononuclear infiltrates. b) Hyperkeratosis, parakeratosis and psoriatic rete ridge elongation with pustules at several levels (arrows), neutrophilic exocytosis, mainly mononuclear perivascular infiltrate, and dilated papillary vessels. Hematoxylin and eosin, original magnification: (A,B) ×100.

Discussion

We believe that the strength of our study is the comparison of both AGEP and GPP by an identical set of histopathological parameters. Both AGEP and GPP represent a dynamic spongiotic pustular process. This presumably starts with dermal edema and a perivascular infiltrate, and this is followed by pustules in different stages of evolution. Because of this evolution, we studied the features of AGEP in erythema and visible pustules. While cGPP develops over time, aGPP represents acute pustule formation on previously uninvolved skin. Differential diagnostic problems between AGEP and GPP particularly arise in the acute phase of GPP.

It is noteworthy that we found small pustules in all biopsies from erythematous lesions of AGEP. In aGPP, pustules were concentrated somewhat deeper in the epidermis than in cGPP. In biopsies from pustular lesions of AGEP, pustules of different sizes were distributed over several levels, probably reflecting the ongoing process with pustules at consecutive stages in one biopsy. Subcorneal pustules, contiguous to intraepidermal ones, were markedly spongiform in AGEP but were generally less prominent than in GPP.[4,19,20,24] Differences in localization and spongiform character of pustules in a biopsy can provide a hint for differentiating AGEP from GPP. Although in AGEP, pustules were generally non-follicular, follicular pustules could sometimes be observed as well. In our experience, follicular pustules do not exclude the diagnosis of AGEP.

Munro micro-abscesses, representing collections of neutrophils within parakeratosis, are generally associated with psoriasis. However, in AGEP we also observed variously sized late-stage (dried) intracorneal pustules that assumed the configuration of Munro micro-abscesses.

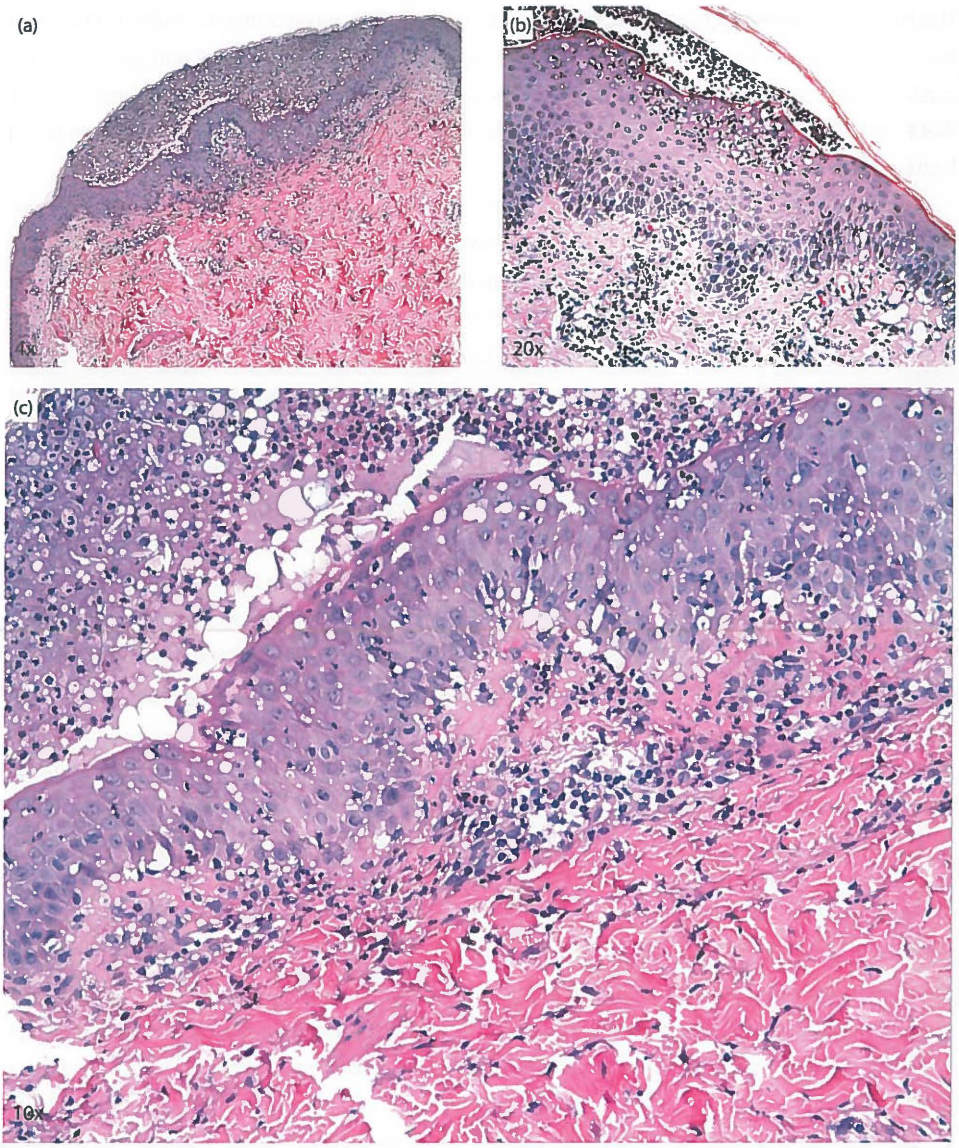

Figure 3. Histopathology of acute generalized pustular psoriasis (aGPP). a) Subcorneal macro-pustule, neutrophilic exocytosis, superficial perivascular, mainly mononuclear, infiltrates with papillary neutrophils. b) Subcorneal/intraepidermal spongiform macro-pustule of Kogoj, neutrophilic exocytosis, slightly psoriasiform rete ridge changes and dilated papillary vessels. c) Detail macro-pustule: neutrophilic exocytosis, papillary neutrophils and superficial perivascular, mainly mononuclear infiltrate. Hematoxylin and eosin, original magnification: (a) ×40, (b) ×200 and (c) ×100.

The higher frequency of Munro micro-abscesses and of other intracorneal pustules in cGPP can be explained by its more protracted course compared with AGEP or aGPP. Spongiform macro-pustules were dominantly present in GPP. Although generally associated with GPP and not with AGEP, those macro-pustules were also regularly (63%) observed in biopsies of AGEP when taken from pustular lesions.

Whether histopathological features of conventional plaque-type psoriasis can be seen in GPP is controversial.[18,25,26] Our study suggests that this controversy is mainly a matter of timing, because psoriatic changes such as hyperkeratosis, parakeratosis, a diminished stratum granulosum, rete ridge changes, elevated mitotic index and suprapapillary plate thinning were far more prominent in cGPP. We believe this is because of its more chronic stage in comparison with aGPP. In aGPP the epidermis was often only slightly acanthotic, as in AGEP. Absent or minor alterations of the stratum corneum, particularly in early lesions of AGEP but also in aGPP, indicate an acute process. Rete ridge change (such as elongation), generally mild, was more frequent in AGEP than generally reported and in our view is apparently less a key point in favor of GPP than previously assumed.[11,18,19] Alterations in rete ridge point to a more developed stage of lesion, since we found them more prominently in pustular than erythematous AGEP lesions (59%), especially when desquamating intracorneal pustules were present. Although substantial psoriasiform changes in a pustular lesion are suggestive of GPP, their absence (such as in aGPP) does not necessarily exclude GPP. On the other hand, minor psoriasiform changes do not rule out AGEP.

While tortuous, dilated vessels were expected in cGPP, we surprisingly also observed them significantly more in aGPP than in AGEP. Moreover, in AGEP they were strongly associated with cases having a personal history of psoriasis (data not shown). Presumably vascular alterations are very specific for psoriasis and are widely present in patients with the disease.

Necrotic keratinocytes, also observed in other drug eruptions, were generally few or scattered outside the pustule in AGEP (88%), while in GPP we hardly found them.[24] On the other hand, lysed keratinocytes within the pustules were more pronounced in GPP, resulting in slightly more spongiform pustules, especially in aGPP.[15,18,25] In AGEP, apoptosis of activated keratinocytes is mainly caused by CD8+ lymphocytes, but CD4+ drug-specific cytotoxic T cells also play a role.[27]

Dermal edema is relatively characteristic (but not specific) for AGEP, especially in its early stages.[16,20] Although less marked than often suggested, moderate to severe papillary edema was present in 40% of biopsies from patients with AGEP, in 29% of biopsies from patients with aGPP and almost absent in biopsies from patients with cGPP.

Eosinophils in pustules, in the dermis and also in the peripheral blood, a hallmark of many drug-induced allergic reactions, suggests that AGEP is a hypersensitivity reaction.[18,28] Although the process of eosinophilic exocytosis was observed in just four biopsies (data not shown), sparse eosinophils were found in 58% of the pustules.[4,16] Dermal eosinophils were more frequent (95%)

although less pronounced than sometimes reported.[4,17,18,22–24] In contrast to AGEP, eosinophils were only found sporadically in GPP.[26]

Remarkably, an interstitial and perivascular mid-dermal infiltrate is not generally considered a feature of AGEP. We found such an infiltrate to be pronounced and mixed, often including numerous neutrophils. In GPP, the infiltrate was less dense, was located more superficially and was mainly mononuclear, while neutrophils were found predominantly in the papillary dermis. We believe these differences in composition and distribution can be diagnostically meaningful.

We regularly noticed erythrocyte extravasation (not generally reported) and mild leukocytoclasia, but alterations suggesting possible vasculitis, including fibrin deposition in the vessel wall, was seen only once in AGEP. Absence of clear evidence for vasculitis in the presence of erythrocyte extravasation and leukocytoclasia has been mentioned before.[20,21] Acute vasculitis in AGEP is sometimes reported in a connection of subepidermal with intraepidermal pustules, which is something we did not observe.[17,24] Overreporting of vasculitis might be caused by interpretation of leukocytoclasia and/or erythrocyte extravasation as vasculitis or by diagnostic confusion with pustular vasculitis. Purpura may occur in AGEP and other drug-induced eruptions, even in the absence of vasculitis.

An earlier clinical study of 63 cases of AGEP, including 64 biopsies from 48 patients, mentions superficial spongiform pustules (66%), focal necrotic keratinocytes (25%), psoriasiform hyperplasia (39%), mixed perivascular infiltrates with eosinophils (34%), papillary edema (61%) and leukocytoclastic vasculitis (20%) including fibrinoid changes (11%).[16] Remarkably, our study showed far more pustules, papillary edema (91%), dermal eosinophilia (95%) and necrotic keratinocytes (88%). This might indicate that biopsies in these two studies were taken at different stages. We found far less fibrinoid alteration, while psoriatic changes were comparable. Differences might also be attributed to case definition, inclusion criteria and use of step sections in our study.

AGEP can also occur in patients with plaque psoriasis. It has been suggested that AGEP merely represents a variant of GPP, and thus signifies an acute exacerbation of psoriasis caused by a variety of exogenous triggers. However, analysis of a subgroup of seven AGEP cases with a known personal history of psoriasis in our study did not show significant differences with the other cases. Also, the observation of several significant differences in GPP vs. AGEP supports the concept that AGEP is a separate entity that can occur as an acute eruption in patients with a history of psoriasis. On the basis of our findings, there are no grounds to assume that an acute pustular rash, occurring in patients with known psoriasis, is necessarily GPP or that AGEP is a variant of pustular psoriasis.

As noticed before, the prevalence of patients with a personal history of psoriasis in our study of AGEP (26.9%) was higher than could be expected from the general population (1–4%).[3,5,16,29,30] This higher prevalence might indicate that patients with GPP and AGEP share a common genetic background, which directs them to react with neutrophil-attracting mechanisms.

The etiopathogenesis of AGEP is still not fully elucidated although some progress has been made. Positive results from patch and lymphocyte transformation tests with the suspected agent, indicating a delayed type IV hypersensitivity reaction, support a drug etiology and the concept that T cells play a crucial role.[21,31] It was recently appreciated that interleukin-8 (IL-8), secreted by T cells and keratinocytes, enhances neutrophilic inflammation and survival, thus leading to sterile pustular lesions.[31,32] Similar mechanisms seem to be relevant for other T-cell-mediated diseases with neutrophilic inflammation, like GPP, which has an underlying tendency for a Th1-dominated immune response.[32-35] Besides, few CXCL8+ T cells displaying a Th2-type cytokine profile with high IL-4 and IL-5 secretions, may contribute to the eosinophilia, regularly observed in AGEP.[32] In GPP, IL-5 is not secreted, which might explain the absence of eosinophilia.[28,36]

Conclusions

In summary, the present study found a spectrum of histopathological features of both AGEP and GPP. Differentiating AGEP from GPP, especially aGPP, presents a clinical and histopathological challenge. Whereas no single histopathological feature is decisive on its own, the combination of features and their grade of severity can substantially contribute to negotiating this differential diagnosis successfully. Features pointing at AGEP instead of GPP include the presence of eosinophils in the pustules or dermis, necrotic keratinocytes, a mixed neutrophil-rich interstitial and mid-dermal infiltrate and the absence of tortuous, dilated blood vessels. Moreover, cGPP showed significant epidermal psoriasiform changes. These key histopathological features, combined with clinicopathological correlation, will assist in differentiation between AGEP and GPP in most instances.

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Acute generalized exanthematous pustulosis caused by morphine, confirmed by positive patch test and lymphocyte transformation test.

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Summary

Morphine, an opium alkaloid, frequently causes side effects such as hyperhidrosis and facial flushing, but serious cutaneous adverse drug reactions are seldom observed. Best known are urticaria, erythema, and pruritus; sometimes pseudoallergic anaphylactoid reactions, and blisters are reported.

Acute generalized exanthematous pustulosis (AGEP) is a serious, mainly drug-induced eruption, generally accompanied by fever and neutrophilic leukocytosis, showing widespread bright erythema studded with many small, nonfollicular pustules.[1-3] We present a patient with AGEP. Time relation, epicutaneous testing, as well as a lymphocyte transformation test (LTT) identified morphine as the culprit.

Case report

A 27-year-old healthy man underwent osteosynthesis because of a fracture of the tibia and fibula of his right leg. His medical history was unremarkable, and he had no personal or family history of skin disease or cutaneous adverse drug reactions (CADR). He received preoperatively subcutaneous nadroparin and one dose of cefazolin. Next day (day 1) fasciotomy was performed because of suspicion for compartment syndrome. On both occasions paracetamol, diclofenac, and morphine were given postoperatively. Morphine was stopped after day 1. On day 10 abdominal and inguinal erythema was noticed, and paracetamol and diclofenac were withdrawn. A few hours later the patient's temperature was 39.4°C. On day 11 he underwent split-skin transplantation. All 3 operations were performed with the patient under spinal anesthesia, for which lidocaine, bupivacaine, ephedrine, midazolam, and mannitol were given. On day 11, postoperatively, his temperature was 38.4°C and for pain prophylaxis one dose of morphine, 10 mg, was given intravenously. A few hours later his temperature was 40.8°C and extending itching and burning erythema was observed. Next day fever rose to 41.2°C and with the suspicion of toxic shock syndrome he was transferred to the intensive care unit and given intravenous gentamicin, followed by dexamethasone, cefuroxime, and metronidazole, and again paracetamol and diclofenac. That day the widespread bright exanthems had numerous tiny nonfollicular pustules, most pronounced in inguinal and axillary areas, but also on the trunk, face, and proximal limbs (**Fig. 1**). On day 13 the patient's fever dropped to 39.2°C. On day 14 the patient felt well, his temperature had abated, and the pustules were clearing. Because clinical and laboratory examinations revealed no infection, a CADR was considered and dexamethasone and antibiotics were stopped. On day 20 he was dismissed, the skin was healing with extensive postpustular desquamation, followed by full recovery within 2 weeks.

Figure 1. Bright generalized erythema, studded with many pinheaded pustules.

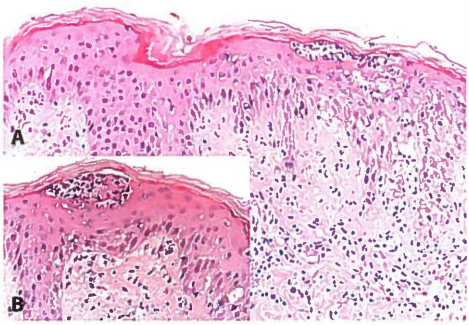

Figure 2. (**A**) Photomicrographs show intraepidermal pustules and spongiosis with mixed perivascular infiltrate spreading into interstitium. (**B**) Intraepidermal pustule with spongiosis and edema in papillary dermis with some leukocytoclasia. (**A** and **B** Hematoxylin-eosin stain; original magnifications: **A** ×10; **B** ×40.)

On day 12 laboratory investigations showed marked leukocytosis (27.6 × 109/L), neutrophilia (25.1 × 109/L), eosinophilia (0.6 × 109/L), and raised levels of aspartate aminotransferase (54 U/L), alanine aminotransferase (83 U/L), erythrocyte sedimentation rate (25 mm/h) and C- reactive protein (185 mg/mL); otherwise his blood chemistry was normal. Gram staining of a pustule, blood and skin cultures, anti–streptolysin O titer, and streptococcal antibodies revealed no microbial involvement. Histologic examination showed spongiosis, spongiform intraepidermal and subcorneal pustules, and focal dyskeratotic epidermal cells. The upper dermis demonstrated papillary edema, a perivascular mixed infiltrate with many neutrophils, some leukocytoclasia, erythrocytes, and eosinophils (**Fig. 2**).

Six months later patch tests were positive for morphine HCl, 10 mg/mL as is (3+) and morphine 1% in an aqueous solution (2+) after 72 hours, while the European Standard Series and all other drugs used perioperatively yielded negative findings.[4] Powderized commercial preparations were tested pure and diluted at 30% in petrolatum and in water; liquids were tested as is.[5] Results from 10 control patients with morphine 1% in aqua were negative.[4] Histologic examination of the positive test showed slight spongiosis and exocytosis of mainly CD8+ lymphocytes with cytotoxic granules and a moderate perivascular lymphocytic infiltrate containing several CD8+ cells. Four months later LTTs in triplicate (for all drugs used perioperatively) demonstrated that morphine had a positive stimulation index of 4.2 for 1 µg/mL, whereas for 100 µg/mL it was 2.3 (positive >2.0).6 All other drugs used perioperatively caused no stimulation. Lymphocytes from a control patient showed no stimulation for morphine. There was no relapse during a follow-up period of more than 2 years.

Discussion

According to a recently developed validation score for AGEP, our patient was a definite case (maximum score of 12).[3] Diagnosis of CADR in patients receiving multiple drug therapy mainly relies on history, if necessary in combination with different tests, as none of the single tests available has sufficient sensitivity per se. In our patient, time relation, positive patch tests, and positive LTTs all confirmed morphine as the culprit. Although cefazolin, paracetamol, and diclofenac are known as offending drugs in AGEP,[2,3] it is unlikely that these were the culprit. One dose of cefazolin was given 10 days before the eruption, and subsequent administration of cefuroxime (another cephalosporin) caused no further exacerbation. Paracetamol and diclofenac, given 10 days before the eruption, were temporarily stopped and reintroduced without complications.

Patch tests can be performed with the pure substance, diluted at 10% in petrolatum and/or water, but generally any commercialized form can be tested as is (facultative) and diluted at 30% in petrolatum and/or in water.[5] In CADR testing of suspected drugs yields positive findings in 32% to 50% of patients. A positive patch test is an indicator of a hypersensitivity reaction, whereas a negative test does not exclude it. The clinical relevance of patch testing depends on the type of CADR and is usually of value in eczematous eruptions, baboon syndrome, macular/papular rash, AGEP, hypersensitivity syndrome, as well as lichenoid and fixed drug eruptions. Positive tests most frequently are related to β-lactam antibiotics, sulfamethoxazole/trimethoprim, corticosteroids, heparin derivatives, carbamazepine, and diltiazem.[5]

The LTT measures proliferation of T cells to a drug in vitro, indicating sensitization. Drugs can directly interact with the T-cell receptor, without previous metabolization or earlier binding to proteins. The LTT has a sensitivity of 60% to 70%; however, this figure is based mainly on analysis of β-lactam sensitivity. A positive LTT helps to define the culprit drug, but negative tests cannot rule out drug hypersensitivity. The LTT has been found positive in generalized macular/papular exanthems, bullous exanthems, AGEP, and hypersensitivity syndrome, but is rarely positive in toxic epidermal necrolysis, vasculitis, macular exanthems, and fixed drug eruption.[6]

In severe CADR, patch testing is relatively safe compared with rechallenge. In one study, 7 of 14 AGEP cases were positive, suggesting that in AGEP sensitivity is relatively high. However, this might also be related to the characteristics of the offending drugs.[7] Positive patch tests for morphine are mainly known from persons handling opium alkaloids, who generally present with contact dermatitis.[8,9] Only rarely have these been described after systemic use of opium alkaloids.[10-12] Given the relatively long interval between the start of morphine and the appearance of the eruption, previous sensitization seems unlikely. Besides, our patient experienced no earlier CADR and had not used or handled opium alkaloids before his presentation to us.

Sporadically positive LTTs have been reported in AGEP, but not for morphine.[13-17] In most of these cases, however, patch tests were negative or not performed.[13,14,16,17]

The pathogenesis of AGEP remains hypothetical. Patch testing may provoke relapses, supporting the idea that the immune system is involved and that a positive test has relevance.[18,19] This reactivation seems to be triggered by a "memory," possibly related to T cells homing in the skin. The positive patch test and LTT are arguments for a delayed type IV hypersensitivity, suggesting involvement of T cells. This is also suggested by the observation that patch tests can mimic the morphologic characteristics of the original skin reaction.[15] In AGEP the infiltration of neutrophils and some eosinophils as well as CD4+ and CD8+ lymphocytes is striking. Drug-specific T-cell clones from lesional skin as well as from the circulation have been found positive for the neutrophil-attracting cytokine interleukin 8. This type of T-cell–mediated neutrophilic inflammation has been coined a type IV-d reaction.[20] Since keratinocytes also show positive staining for interleukin 8 in lesional skin in AGEP, these cells appear to participate in the neutrophilic attraction.[20]

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Acute generalized exanthematous pustulosis (AGEP), presenting with toxic epidermal necrolysis–like features, a neglected culprit?

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For severe backache, a 70-year-old female started naproxen and omeprazole, replaced by morphine 10 mg two days later. History revealed stable psoriasis, treated by local corticosteroids, and an earlier serious cutaneous adverse reaction (cADR), resembling toxic epidermal necrolysis (TEN), ascribed to azapropazone. Eight days after starting morphine, an increasing erythematous rash developed, preceded by fever.

On admission, one day later, we observed widespread oedematous erythema, accentuated on the main flexures, but also on the face, studded with many tiny pustules and superficial erosions at sites of extensive coalescence of pustules. Arthritis and mucosal involvement were absent. TEN, pustular psoriasis, acute generalized exanthematous pustulosis (AGEP) and infection were considered; prednisolone 40 mg and erythromycin 500 mg QID were initiated and morphine was switched to tramadol 100 mg TID. Laboratory examinations revealed elevated C reactive protein (154 mg/L), leukocytosis (13.6×10^9/L), and neutrophilia (11.4×10^9/L), but were otherwise normal. Investigations for infections were negative, including anti-streptolysin O titre and bacterial cultures (pustule and throat). Histology showed slightly spongiform subcorneal pustules, neutrophilic spongiosis, a few necrotic keratinocytes, dermal oedema and mixed neutrophil-rich infiltrates, both perivascular and interstitial. TEN-like features such as extensive keratinocyte apoptosis and subepidermal blistering were absent (**Fig. 1 D**).Three days later, improvement started with postpustular desquamation, while superficial erosions and some pustular lesions were still present (**Fig. 1A, B**), followed by rapid healing within 2 weeks. During an 18 month follow-up there was no recurrence.

According to the criteria of Sidoroff *et al.*[1] definite AGEP was established. AGEP is mainly induced by drugs and characterized by the sudden appearance of dozens of sterile, non-follicular, small pustules on oedematous erythema with a widespread distribution or predilection for the face and/or skin folds. Coalescence of pustules in AGEP may result in superficial erosions, suggesting TEN, histopathology however is discriminative. Pustular psoriasis was thought unlikely because of the abrupt onset, short duration, association with recently started drugs and full, quick recovery after their elimination, and non-recurrence. Of note, AGEP has been reported before in patients with a history of psoriasis and more frequently than could be expected in the general population.[2,3] Moreover, histology favoured AGEP over pustular psoriasis, showing some necrotic keratinocytes and mixed neutrophil-rich interstitial and mid-dermal infiltrates, whereas significant epidermal psoriasiform changes were lacking.[3]

Patch testing was performed three months later, including all the drugs the patient had been exposed to, using their commercialized form.[4] The European standard series, naproxen and omeprazole pure pulverized, 30% in aqua and 30% in petrolatum, and morphine pure pulverized gave negative test results; pulverized morphine 30% in aqua, 30% in petrolatum (**Fig. 1C**), and morphine 1% solution in aqua showed a 3+ reaction with erythema and pustules after 96hours, while in 10 controls all morphine tests were negative. Histology of a positive patch test revealed subcorneal pustules, neutrophilic spongiosis, scattered apoptotic keratinocytes, dermal oedema and mixed dermal infiltrates, a picture compatible with AGEP (**Fig. 1E**).

Remarkably, the patch test resembled the original eruption both clinically and histologically; pustular test results have been described before. Patch testing, more often positive in AGEP compared to other cADR, contributes to identification of the culprit and to narrowing down differential diagnoses in ambiguous cases.[4,5]

In conclusion, we describe the third case of AGEP induced by morphine, the second confirmed by positive patch tests.[5,6] Morphine, regularly used, often short-term in the peri-operative situation or for chronic pain relieve, has a rather safe profile concerning cADR, which include pruritus, erythema, urticaria and flushing. Although rarely associated with AGEP, morphine should not be overlooked as a potential culprit.

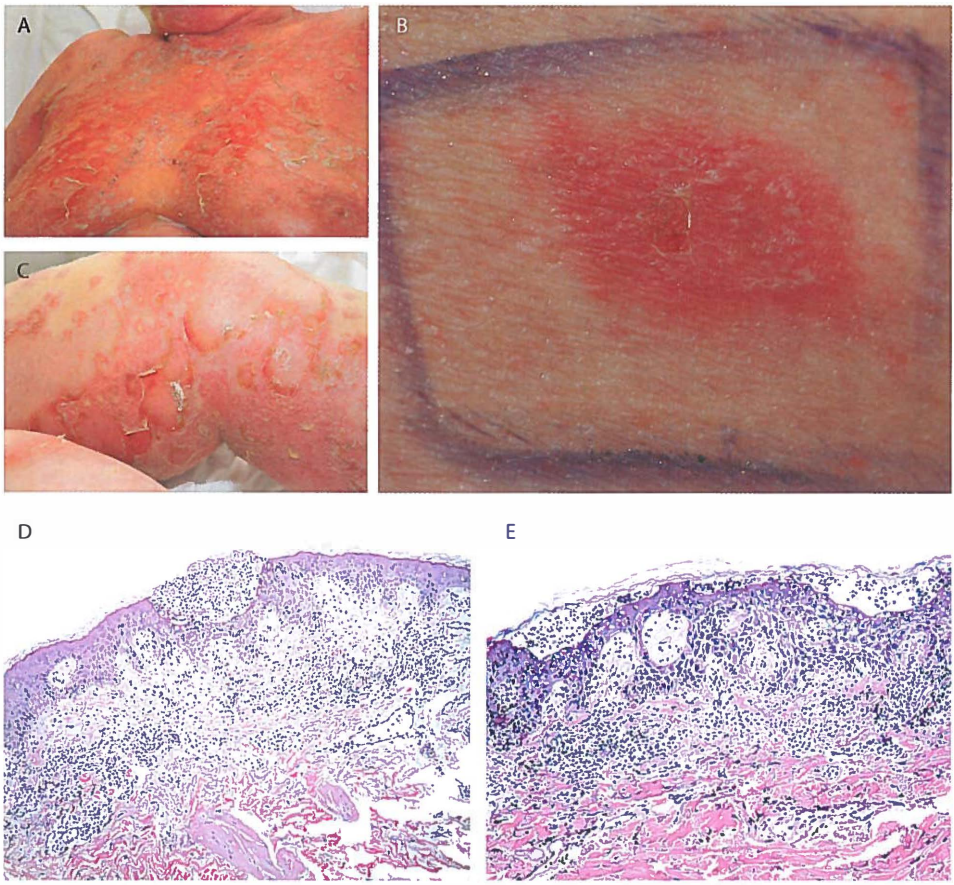

Figure 1 A) Extensive oedematous erythema accentuated in the main folds with desquamating superficial erosions and some pustules; **B)** oedematous erythema with extensive coalescence of pustules resulting in superficial erosions; **C)** patch test showing oedematous erythema with tiny pustules; Histopathology **D)** (pustule abdomen) and **E)** (positive morphine patch test at 96hours): subcorneal slight spongiform pustules, a few necrotic keratinocytes, neutrophilic spongiosis, papillary oedema and mixed neutrophil-rich superficial and middermal perivascular and interstitial infiltrates. Hematoxylin and eosin, original magnification ×10.

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Symmetrical drug-related intertriginous and flexural exanthema (baboon syndrome) induced by omeprazole.

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Editor,

We describe two cases of symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) with remarkable cutaneous symptoms, slight systemic involvement, and a relative long latency time, caused by omeprazole.

A 67-year-old woman demonstrated symmetric, confluent erythematopapular lesions on inner gluteal areas, groins, and neck, accompanied by itching, burning, and a feverish feeling, 17 days after starting omeprazole. Two days later, omeprazole was discontinued, and a short course of prednisolone was given. The gluteal rash improved, while on the neck it worsened (**Fig. 1a**). Mometasone ointment, 9 days after discontinuing omeprazole, resulted in rapid healing. The patient had no co-medication, previous use of omeprazole, or history of cutaneous adverse drug reactions (cADR). Histopathology showed small intra/subcorneal pustules, slight epidermal spongiosis, and vacuolar degeneration with moderate, mainly superficial, perivascular infiltrates, with some neutrophils and eosinophils (**Fig. 1b**). Patch tests with omeprazole were negative.

The second case, a 27-year-old woman, started omeprazole for stomach ache during methotrexate maintenance therapy, 15 mg weekly. At day 6, intense itching and increasing flexural redness developed. At day 9, she presented with symmetric, sharply demarcated, bright erythema, studded with several tiny non-follicular pustules on the buttocks, inguinal extending to the upper-inner thighs and anogenital, axillary, and (sub)mammary areas (**Fig. 2**). Furthermore, faint erythematous upper eyelids and few pinpoint blanchable erythematous macules on the ventral side of wrists and hands were observed. For psoriasis vulgaris, she had received methotrexate for four months, while local treatment consisted of desoximetasone emulsion for the scalp and emollient. Except for the scalp, the psoriasis was in remission; fever, malaise, and arthritis were absent. Laboratory investigations were normal, except for slightly elevated alanine transaminase (88 U/l), eosinophils (5.7%) and neutrophils (80.6%), with leukocytes 5.4 × 10^9/l. Pustular swabs revealed no yeasts or bacteria. Omeprazole was stopped, and clemastin 1 mg and triamcinolone acetonide in ketoconazole cream were started. One day later progression halted; the eruption was resolved within two weeks. The patient refused patch testing.

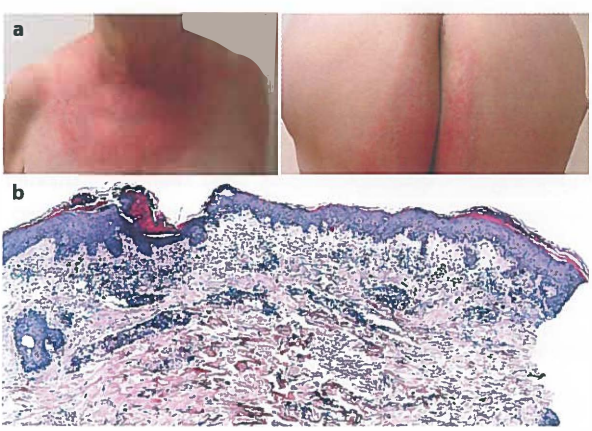

Figure 1. (a) Large, rather sharply demarcated, confluent erythematopapular lesions in the neck spreading to the upper chest and on the inner gluteal areas. (b) Histology of the neck (H&E, original mafgnification x 40): small intra-/subcorneal pustules and moderate, mainly superficial perivascular infiltrates also containing neutrophils and sporadic eosinophils

SDRIFE, a benign, probably underreported cADR with male predominance, is supposedly homogenous for the range of primary cutaneous lesions, clinical distribution (excluding face and palmae), and latency period. Particularly amoxicillin and other β-lactam antibiotics are held responsible.[1]

Diagnostic criteria are systemic drug exposure, sharply demarcated erythema of the gluteal/perianal and/or V-shaped erythema of the inguinal/perigenital area, involvement of more than one other intertriginous/flexural fold, symmetric distribution, and absence of systemic symptoms and signs.[1] Distribution and characteristics of the lesions in both cases were typical for SDRIFE.[1,2] However, of note was the extensive participation of the neck in patient 1, and pustules, widespread intertriginous and flexural involvement, and facial and palmar participation in patient 2. Although the absence of systemic involvement is a criterion for SDRIFE, we noted a feverish feeling in one and a mild disturbed liver function, eosinophilia, and neutrophilia in the other.[2,3] Characteristic is a latency period of hours to days after drug initiation, but longer periods (17 and 5 days in our cases) may occur, depending on drug- and patient-related factors.[1,2,4,5]

The histopathology of SDRIFE is variable and non-specific, mainly showing superficial, mononuclear perivascular infiltrates, sometimes with neutrophils and eosinophils.[1,2] Patient 1 also displayed small intra/subcorneal pustules.[1,2]

Pustules in SDRIFE (patient 2 and, histopathologically, patient 1) necessitate differentiation from acute generalized exanthematous pustulosis (AGEP).[1,2] Both also share a short latency period, flexural affection, potential immunological pathogenesis, including neutrophilic involvement, and potential culprits. However, AGEP was unlikely considering the absence of disseminated erythema, high fever, neutrophilia >7 × 10^9/l and, histopathologically, papillary edema and necrotic keratinocytes.[6,7] Distribution of the sharply demarcated lesions, quick recovery after omeprazole withdrawal, absence of psoriatic activity, fever and arthritis, and the presence of transient eosinophilia make pustular psoriasis unlikely in patient 2.

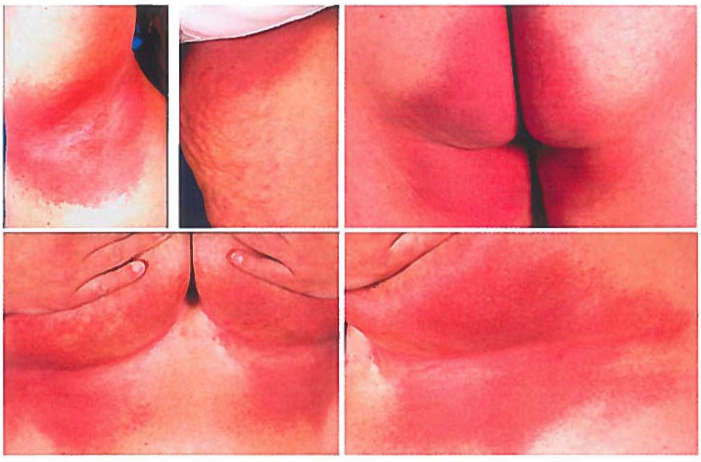

Figure 2. Symmetric, rather sharply demarcated, bright erythematous lesions on the axillary, inguinal, (sub)mammary, and inner gluteal areas and buttocks, studded with several tiny pustules

The etiology of SDRIFE is not yet elucidated. Occlusion, sweating or mechanical injury, or a type of recall phenomenon of a past, unrelated dermatitis, occurring in precisely the same areas, have been postulated.[1,4,8] Patch tests in SDRIFE can be positive; a type IV delayed-hypersensitivity immune response is presumed. In a review of 42 cases, 12 out of 24 showed positive drug patch test results.[1]

Omeprazole, a potent and widely used proton pump inhibitor, is a prodrug and usually well tolerated. Although rare and most often mild, omeprazole has been associated with a variety of cADR, especially non-specific rashes, anaphylaxis, urticaria, angioedema, edema, and pruritus. However, also lichenoid eruptions, leukocytoclastic vasculitis, toxic epidermal necrolysis, contact dermatitis, and alopecia have been mentioned.[9,10]

In conclusion, we describe two females with SDRIFE, induced by omeprazole, a drug not appointed before. Fulfilling basic characteristic criteria of SDRIFE, both cases additionally revealed remarkable uncommon features. SDRIFE may display less homogeneity than suggested by the strict diagnostic criteria.

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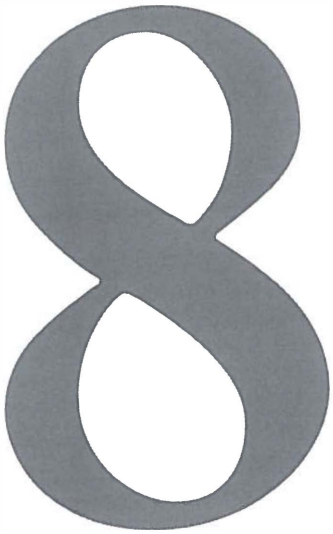

Erlotinib-induced florid acneiform rash complicated by extensive impetiginization.

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Summary

Erlotinib (Tarceva™) is an epidermal growth factor receptor (EGFR) inhibitor, a member of a new group of molecular targeted drugs that combine high efficacy against tumours with less, often self-limiting, toxicity, compared with traditional chemotherapeutics. It is used for treatment of solid-organ tumours, especially as second- or third-line therapy for non-small-cell lung cancer. Dose-related cutaneous side-effects and diarrhoea may be a significant obstacle to treatment compliance. We present two cases with long-lasting acneiform eruptions, complicated by significant impetiginization, resulting in hospitalization in one case. The other patient suffered from sleep-disturbing, itching crusts on the scalp. As the use of EGFR inhibitors is increasing, clinicians should be aware of their side-effects. Early and timely dermatological intervention may diminish adverse events for patients treated with these agents and improve quality of life.

Acneiform eruptions are common side-effects of erlotinib (Tarceva™), an epidermal growth factor receptor inhibitor that is increasingly being used in the treatment of solid-organ tumours. Generally, side-effects are dose-dependent and self-limiting. We report two patients with long-lasting acneiform eruptions, complicated by significant impetiginization. Proactive dermatological intervention can improve compliance and quality of life for patients on EGFR inhibitors.

Case reports

Patient 1. A 74-year-old white man started erlotinib monotherapy 150 mg for progression of stage IIIB non-small-cell lung cancer (NSCLC) after earlier lobectomy and chemotherapy. Within days pustules developed, followed by dry skin. Five weeks later, the patient presented with sterile, widely dispersed, inflammatory follicular papulopustules, predominantly in the seborrhoeic areas, and dry skin with slightly erythematosquamous lesions on the face, arms and legs. Erythema with maceration of the groins was treated with triamcinolone in ketoconazole cream. One week later, the patient was hospitalized for malaise, subfebrile temperature, increasing diarrhoea, otitis externa, ectropion and purulent conjunctivitis. The skin was painful, with extensive, partly oozing erythema and yellowish crusts mainly extending from the body folds, causing disability in walking (**Fig. 1a,b**). We diagnosed erlotinib-induced acneiform rash and xerosis cutis with extensive secondary impetiginization.

Blood investigations were normal except for slightly raised erythocyte sedimentation rate, C-reactive protein and eosinophils (5.2×10^9/L). Pustules revealed *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*; tests on faeces were negative. Histology showed spongiform pustules, dermal perivascular lymphoid infiltrates with some neutrophils and eosinophils, and a folliculitis in deeper sections (**Fig. 1c**). Local silver sulfadiazine, zinc oil, antibacterial baths, ear and eye drops, neutral emollients, and systemic amoxicillin/clavulanic acid resulted in rapid improvement. Increasing diarrhoea required interruption of erlotinib for 12 days, during which all symptoms improved. Erlotinib was restarted at 50 mg/day and gradually raised with minocycline 100 mg and continuing emollients. Ten days later, the patient experienced mild diarrhoea, as well as erythema on the face and groins, which improved after silver sulfadiazine cream twice daily. Residual maculopapules on the trunk gradually faded away.

Figure 1. (a) Acneiform eruption with partly oozing erythema; (b) ectropion and erythema with yellowish crusts on the face; (c) a dermal mixed perivascular lymphoid infiltrate and folliculitis (haematoxylin and eosin, original magnification x 40).

Patient 2. A 55-year-old white man started erlotinib 150 mg/day for stage T2N2M0 NSCLC after earlier lobectomy, chemotherapy, and radiotherapy. Four months later, he presented with a 4-week history of progressive, severely itching, sleep-disturbing, yellowish crusts, firmly attached to the scalp (**Fig. 2a**). We also noticed dry skin and generalized acneiform follicular lesions, mainly located in seborrhoeic areas. Laboratory investigations showed no abnormalities except slight eosinophilia (3.2×10^9/L). Histology of the trunk revealed neutrophilic infiltration of the infundibular and deeper follicular wall, with superficial follicular dilatations containing denaturated keratin and some yeasts (**Fig. 2b**); the scalp showed epidermal ulceration with neutrophils and extensive, deeply extending mixed infiltrates. Minocycline 100 mg/day for 7 days, salicylic acid 7.5% in castor oil, bath oil, emollients, and hydroxyzine 10 mg nightly resulted in rapid improvement. Stopping minocycline caused the crusts to worsen. Because *S. aureus* was cultured, cefradine was given for 10 days. Minocycline was restarted, which maintained improvement (**Fig. 2c**).

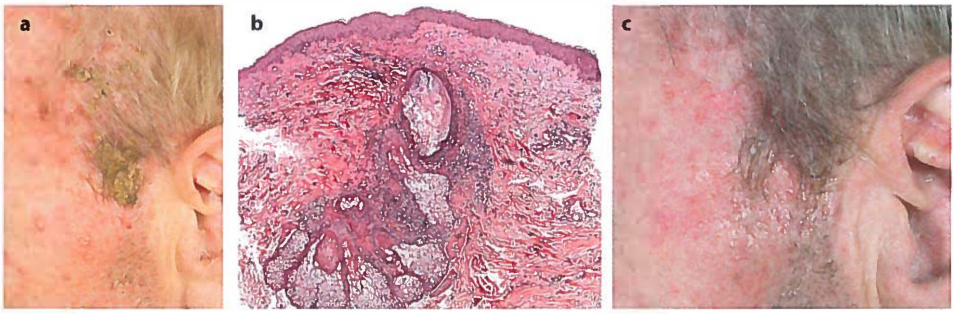

Figure 2. (a) Acneiform eruption and yellowish crusts on the scalp; (b) superficial follicular dilations containing denaturated horn and neutrophilic infiltration of the follicle wall (haematoxylin and eosin, original magnification x 40); (c) improvement after 7 days on minocycline.

Discussion

Erlotinib, an oral reversible intracellular tyrosine kinase inhibitor that blocks downstream signalling pathways for cellular proliferation and differentiation, is used as monotherapy or in combination with other chemotherapeutics for several solid tumours. This EGFR inhibitor has an established role in the treatment of advanced, refractory NSCLC.[1,2]

EGFR is expressed in proliferating undifferentiated basal epidermal keratinocytes, eccrine and sebaceous glands, the outer follicular root sheath, the respiratory system and the gastrointestinal tract.[3] Because dysregulated EGFR expression is associated with aggressive tumours, increased resistance to chemotherapy and radiotherapy, and poor clinical prognosis, new chemotherapeutics focus on EGFR inhibition.[1,4,5]

The maximum tolerated dose of continuous administration is 150 mg/day.[5] Generally mild, dose-dependent, and self-limiting side-effects are seen, particularly acneiform rashes and diarrhoea. Others include painful fissures on the palms and soles, paronychia, dry skin, eczema, mucositis, conjunctivitis, nausea, vomiting, malaise, alopecia, slower growing and/or brittle hair, and trichomegaly.[6–8] Rare but severe side-effects are interstitial lung disease and corneal ulceration. Marked haematological effects are absent.[1,4,6]

Within 8–10 days on average, a mild or moderate acneiform eruption without comedones, characterized by numerous monomorphic, sterile, sometimes itching, inflammatory follicular papulopustules, mainly in seborrhoeic areas, occurs in most patients; in 5–10%, this reaction is severe.[1,4–9] Maximum intensity is reached within 3 weeks. Despite continued treatment with erlotinib, the reaction often gradually subsides.[5,6,9] A similar eruption is also often seen with other EGFR inhibitors (cetuximab, gefitinib), and shows similar histology, with neutrophilic dermal infiltrates, neutrophilic (peri)folliculitis, and ectatic appearance of the infundibula, indicating a class effect.[5,7–9] Sometimes a suppurative superficial folliculitis, like that in patient 1, is observed.[8] After several weeks, xerosis cutis may develop, predominantly on the arms, legs, and areas previously affected by the acneiform eruption, sometimes resulting in secondary infection.[7] For erlotinib and the related gefitinib, we did not find any reports of eosinophilia.

The mechanism of the rash is unknown, but points to an imbalance in differentiation and maturation causing secondary inflammation.[7] EGFR blockade increases expression of proinflammatory chemokines and $p27^{Kip}$,[1] a negative growth regulator enhancing apoptosis and promoting keratinocyte differentiation.[3,8] This may lead to a thin stratum corneum and inflammatory infiltration of the follicles, which often become dilated and plugged by excessive keratin, occasionally with microorganisms as observed in patient 2.[5,7,8]

Treatment of the eruption is not yet standardized. Because some studies suggest that the presence and severity of the eruption correlates with response and prognosis, and because it is often self-limiting, side-effects should not necessarily be an indication to discontinue treatment.[1,2,8] Systemic antibiotics, especially tetracyclines (mainly for anti-inflammatory effects), should be considered for severe acneiform eruptions.[7] They can quickly be discontinued in some, but in others, continued treatment is required.[2,10] Local antibiotics, antimycotics, emollients, retinoids and corticosteroids have produced variable responses.[1,7–10] To prevent bacterial superinfection, care should be taken when using steroids.[8]

Both of our patients experienced long-lasting widespread acneiform eruptions and xerosis cutis, probably rendering them susceptible to infection, resulting in acute oozing and hospitalization in case 1.[7] Patient 2, in contrast to most reports, had extensive scalp involvement, in which aggregation of dried-out pustules may have formed yellowish crusts.[7,9] Because both patients experienced a widespread pustular rash, acute generalised exanthematous pustulosis could be considered. However, the less acute and follicular presentation and the absence of neutrophilia argue against this diagnosis.

Oncologists and dermatologists should actively communicate and cooperate to recognize side-effects that are secondary to the direct inhibitory effect of EGFR inhibitors on the epidermis and pilosebaceous follicle. Proactive dermatological intervention can improve compliance and quality of life in these patients.

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Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist?

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SIR, In a recent study Peyrière *et al.*[1] stated that the existence of a clinical entity, known under various names including HSS (anticonvulsant hypersensitivity syndrome), DRESS (drug reaction with eosinophilia and systemic symptoms), DIDMOHS (drug-induced delayed multiorgan hypersensitivity syndrome) and DIHS (drug-induced hypersensitivity syndrome) cannot be denied but that its definition, clinical and biological pattern, and limits must be more accurately reappraised. We can fully endorse that a gold standard is lacking, as is also repeatedly stated in the literature. Also the lack of consensus on nosology is obvious, but this is minor if there is agreement on what are the main characteristics of the 'syndrome'. Although it is generally accepted that a syndrome by its nature comprises a variable combination of symptoms, the acronym DRESS is questioned as eosinophilia need not necessarily be present in this syndrome.

The diversity of cutaneous adverse drug reactions is nearly infinite. It makes sense to isolate syndromes, rather than to consider the whole as a continuum, if it helps in finding original clinical patterns, courses, causes, mechanisms and treatment. From long discussions between experts from different countries in recent medical meetings on drug hypersensitivity it appears that whatever the denomination, HSS/DRESS is characterized by a variable combination of: (i) drug-induced immunological background; (ii) later onset than other drug reactions; (iii) longer duration than common 'drug rashes'; (iv) multiorgan involvement; (v) lymphocyte activation (node enlargement, lymphocytosis, atypical lymphocytes); (vi) eosinophilia; and (vii) frequent virus reactivation.

HSS/DRESS is specifically complicated because besides its rather variable presentation it is a diagnosis by exclusion. Its main features such as rash, fever and organ involvement can also be attributed to a wide range of other causes such as infections, and to concomitant and pre-existing diseases. Hence each symptom should always be thoroughly investigated for its relation to the syndrome. Not all symptoms and signs are always recognized, and asymptomatic systemic involvement such as eosinophilia and atypical lymphocytes are often not determined or are determined too late, leading to their under-reporting. In addition, partly due to the relatively long latency after initiation and the long duration after cessation of the culprit drug, the symptoms are often not recognized as drug related. General awareness of HSS/DRESS is very important due to the severity and life-threatening potential of this type of drug reaction.

The RegiSCAR study group (as its predecessors EuroSCAR and SCAR) is performing a prospective study of severe cutaneous adverse reactions (SCAR) in Austria, France, Germany, Israel, Italy and the Netherlands, in order to investigate their risk factors and mechanisms based on a large multinational registry. Former projects of the group dealt with the spectrum of Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)[2] and acute generalized exanthematous pustulosis (AGEP).[3] Crucial to these studies has been a clear case definition. The combination of a scoring system and judgement of cases by a review committee (blinded for possible risk factors) has proven effective for validation in SJS/TEN and AGEP. The group's intention to extend investigations to HSS/DRESS raised the need for an equally reliable approach for those cases.

RegiSCAR has collected cases of HSS/DRESS since 2002. Patients are actively detected through a hospital network covering about 170 million inhabitants, using selected inclusion criteria (**Table 1**). Information on reported cases of HSS/DRESS is obtained by trained local interviewers using standardized questionnaires, comprising elaborate questions on drug use, morphology and extent of the rash, involvement of lymph nodes and other organs, laboratory and clinical parameters to judge organ involvement as attributable to HSS/DRESS, and course of the disease. Where possible, clinical pictures and results of histological examination in the active phase of the eruption are collected. Interviews take place at the acute stage of the disease with a follow up at 8 ± 2 weeks and 1 year, if the patient's informed consent for participation in a cohort is obtained. In addition, blood samples are taken for immunological and genetic research.

Table 1. Inclusion criteria for potential case of HSS/DRESS in RegiSCAR

Hospitalization
Reaction suspected to be drug related
Acute skin rash[a]
Fever above 38 °C[a]
Enlarged lymph nodes at at least two sites[a]
Involvement of at least one internal organ[a]
Blood count abnormalities
Lymphocytes above or below the laboratory limits[a]
Eosinophils above the laboratory limits (in percentage or absolute count)[a]
Platelets below the laboratory limits[a]

[a]Three or more required.

Due to the complexity and variability of HSS/DRESS, interpretation of clinical findings and laboratory data by an unorganized reviewing process would not have produced consistent results. Based on information from the literature and clinical experience of the review committee we reached consensus on a scoring system for our study which would allow for reproducibly classifying cases as definite, probable, possible or no case. Thorough case assessment was done on the basis of clinical pictures and analysis of the collected data by experienced clinicians, as this cannot be replaced by a scoring system alone, but will always need professional judgement. An overview of the scoring system is given in **Table 2**. To prevent bias, the review committee was blinded to the suspected drugs.

Although we are aware that virus reactivation may play a role in the syndrome, we do not count the related organ in case of a positive virus serology. However, it is still a matter of debate whether reactivation of several herpesviruses in the course of the disease is part of the syndrome or should be interpreted as a complication, resulting in a more protracted and relapsing disease.[4,5]

In pharmacovigilance, data are often only received retrospectively, whereas we most often see the patient in the acute stage of the disease and systematically collect far more detailed data, permitting us better to judge the presented symptoms. Moreover, the advantages of the scale of our multinational study over a national one, as proposed by Peyrière *et al.*,[1] in a rare syndrome such as HSS/DRESS, are obvious.

Table 2. Scoring system for classifying HSS/DRESS cases as definite, probable, possible or no case

Score	−1	0	1	2	Min.	Max.
Fever ≥ 38·5 °C	No/U	Yes			−1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia		No/U			0	2
Eosinophils			$0·7–1·499 \times 10^9\ L^{-1}$	$\geq 1·5 \times 10^9\ L^{-1}$		
Eosinophils, if leucocytes $< 4·0 \times 10^9\ L^{-1}$			10–19·9%	≥ 20%		
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement					−2	2
Skin rash extent (% body surface area)		No/U	> 50%			
Skin rash suggesting DRESS	No	U	Yes			
Biopsy suggesting DRESS	No	Yes/U				
Organ involvement[a]					0	2
Liver		No/U	Yes			
Kidney		No/U	Yes			
Lung		No/U	Yes			
Muscle/heart		No/U	Yes			
Pancreas		No/U	Yes			
Other organ		No/U	Yes			
Resolution ≥ 15 days	No/U	Yes			−1	0
Evaluation of other potential causes						
Antinuclear antibody						
Blood culture						
Serology for HAV/HBV/HCV						
Chlamydia/mycoplasma						
If none positive and ≥ 3 of above negative			Yes		0	1
Total score					−4	9

U, unknown/unclassifiable; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

[a]After exclusion of other explanations: 1, one organ; 2, two or more organs.

Final score < 2, no case; final score 2–3, possible case; final score 4–5, probable case; final score > 5, definite case.

We anticipate our case definition and system of validation will lead to a reliable identification of cases of HSS/DRESS for further studies of pharmacoepidemiological and genetic risk factors, as well as the immunological background. We expect to be able to answer several long-standing questions after further case enrolment in 12–18 months.

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Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study.

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Under revision.

Summary

Background: Cases of severe drug hypersensitivity, demonstrating a variable spectrum of cutaneous and systemic involvement, are reported under various names, especially DRESS (drug reaction with eosinophilia and systemic symptoms). Case definition and overlap with other severe cutaneous adverse reactions (SCAR) are debated.

Aim of the study: Analysis of the spectrum of signs and symptoms of DRESS and distribution of causative drugs in a large multicenter series.

Patients and methods: RegiSCAR, a multinational registry of SCAR, prospectively enrolled 201 potential cases from 2003 to mid 2009. Using a standardized scoring system, 117 cases were validated as probable or definite DRESS.

Results: The male/female ratio was 0.77; females were significantly younger than males. Next to ubiquitous exanthema, main features were eosinophilia (95%), visceral involvement (91%), high fever (90%), atypical lymphocytes (67%), mild mucosal involvement (56%) and lymphadenopathy (54%). The reaction was protracted in all but 3 cases; 2 patients died during the acute phase. Drug causality was plausible in 88% of cases. Antiepileptic drugs were involved in 36%, allopurinol in 18%, antimicrobial sulfonamides and dapsone in 12% and other antibiotics in 11%. Mean time interval after drug intake was 25.9 ± 19.1 days for all drugs with (very) probable causality, with differences between drugs.

Conclusion: This series supports that DRESS is an original phenotype among SCAR in terms of clinical and biological characteristics, causative drugs, and time relation. The diversity of inciting drugs was rather limited, and mortality was lower than suggested by prior publications.

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS), a rare but potentially life threatening adverse drug reaction (ADR) is characterized by a variable combination of symptomatic and asymptomatic features, both in time and course.[1] Commonly reported features are multi-organ involvement, lymphocyte activation (lymph node enlargement, lymphocytosis including "atypical" activated lymphocytes), eosinophilia, reactivation of herpes viruses, later onset and longer duration than other cutaneous adverse drug reactions (cADR), and a drug-induced aetiology.

The syndrome, first ascribed to aromatic antiepileptic drugs (AED), has been reported under various names, including anticonvulsant hypersensitivity syndrome, drug induced hypersensitivity syndrome (DIHS), DRESS or names referring to the causative drug, the most prominent affected organ or the disease mimicked.[2-5] Since the word hypersensitivity is rather uninformative and ambiguous, the more informative and clinically relevant acronym DRESS is gaining use.

Besides AED, many other drugs have been reported to be associated, such as sulphonamides, allopurinol, minocycline, mexiletine and dozens of other drugs.[1,6-8] The estimated risk at first or second prescription of AED is 1-4.5 in 10,000.[9] The onset is rather delayed, often 2 to 8 weeks after introduction of the inciting drug, although rechallenge can result in a reaction within hours to days.[1,4,10-13] Recovery after withdrawal of the culprit is often complete, but symptoms may persist for weeks to months.[12] Mortality rates of about 10% are regularly reported.[1,12-16]

DRESS is quite a challenging diagnosis, reached after exclusion of other diseases. Diagnosis can be delayed or go unrecognized as drug related because of the variable presentation, course, and severity, relatively late onset, gradual evolution and long duration, even after cessation of the culprit, or because of clinical similarity to infections, collagen vascular or lymphoproliferative diseases.

Knowledge on DRESS mostly relies on case reports and retrospective series, often originating from dermatologists because skin involvement is one of the first and most frequent symptoms noticed.[1,2,4,15-18] At onset, the eruption is often morbilliform and indistinguishable from ordinary drug eruptions or viral rashes. Facial oedema is regularly observed and the eruption may become widespread and polymorphous.[1,2,4] Because the severity of the skin eruption does not necessarily reflect that of the overall reaction, involvement of liver, kidney, lung, and other visceral organs requires independent assessment. Notwithstanding general agreement on the main characteristics of the syndrome, its definition, clinical and biological features needs more accurate appraisal.

Complete pathogenesis is not yet understood and appears to be complex, combining delayed immunologic reactions to drugs, a transient state of immune suppression and

reactivation of latent herpes virus infections.[5,19-21] A genetic predisposition was observed in Han Chinese, with a 100% association between allopurinol induced DRESS and HLA-B*5801.[22]

Because clear case definition including cut-off points of abnormal biological and laboratory values was lacking, and in order to obtain a homogenous cohort of patients for further study, the RegiSCAR study group developed a diagnostic validation score, combining clinical and biological criteria for validating potential cases of DRESS as definite, probable, possible, or no case (appendix).[23] We present the first large prospective series of 117 cases, collected by the RegiSCAR group, validated probable or definite DRESS according to this score.

Patients and methods

Setting

RegiSCAR, a multinational registry of severe cutaneous adverse reactions (SCAR), conducts a prospective, ongoing pharmaco-epidemiological study on Stevens Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), and DRESS, including collection of biological samples, since 2003. Through a network of hospitals in Austria, England, France, Germany, Israel, Italy, Taiwan, and The Netherlands about 120-150 million inhabitants are covered. The study has been approved by the ethical committee of each participating national centre.

Recruitment of cases

Hospitalized patients, notified to the national investigators and meeting three or more of the inclusion criteria (acute rash, fever above 38° C, enlarged lymph nodes on at least two sites, involvement of at least one internal organ, or blood count abnormalities), are consecutively enrolled as potential cases of DRESS.[23] After informed consent and using a structured, reaction-specific questionnaire, trained interviewers collect detailed data on morphology and extent of the rash, clinical and biological data on organ involvement, course of the disease, concomitant/ earlier diseases and infections, and exposure to medication.

Validation of cases

Based on clinical photographs, histopathology, and completed questionnaires with clinical and biological information, but without information on drug exposure and other risk factors, an international expert committee validates potential cases as definite, probable, possible or no case, following a standardized procedure and scoring system (appendix).[23] Signs and symptoms are only attributed to DRESS after exclusion of alternative causes.

Assessment of drug causality

Evaluation of drug causality was an expert decision by consensus between 3 authors (SHK, MM, JCR). A first selection, blinded for name and indication of drugs, was based on the time relation between onset of the reaction and initiation and withdrawal of each drug. The probable index-day, representing the most likely onset of the reaction, is defined as the earliest date of a clinical sign or symptom consistent with a continuum in the disease. Latency was defined as the number of days between initiation of medication with a probable or very probable causality and the probable index-day. Drugs taken long term (>3 months), or stopped >14 days before or initiated <3 days before the probable index-day, were considered unlikely. Prior use without cADR decreased suspicion, while an earlier reaction made the drug a first rank suspect. Hereafter, remaining suspects were unblinded and evaluated according to a list of notoriety for eliciting DRESS, based on literature review. Causality in cases with a single remaining drug was considered "very probable" in presence of highly notorious medication, and "probable" when medication was not notorious or had low notoriety. For cases with several remaining drugs, those with high notoriety were considered "probable" and those with low notoriety possible. Causality in cases with concomitantly used drugs without notoriety was classified as undetermined.

Data management and statistical analysis

All collected data are entered by investigators into a centralized data base (Oracle, version 8.1.7 (8i), Redwood Shores, CA, USA) at the University Medical Center Freiburg, Germany, using the internet based remote-data-entry system MACRO (version 3.0, InferMed, London, UK). For subsequent data processing (including regular data checks, data preparations and data analyses), the software package SAS (version 9.2, Cary, NC, USA) is used. For statistical analysis, the software package SAS, SPSS (version 16, SPSS, Chicago, IL), and MS Excel Data Analysis were used. Categorical/dichotomous variables are presented in absolute numbers and percentages, while mean and standard deviation or, if more appropriate, median and interquartile range are presented for continuous variables. For testing differences between groups, we used the non-parametric Wilcoxon test for continuous variables and Chi-square test for categorical variables assuming a two sided 5% significance level.

Results

Inclusion

Between February 2003 and May 2009, a total of 201 potential cases of DRESS was included. Of these, 27 were validated no case, 56 possible, 59 probable, and 59 definite cases of DRESS. With exception of one probable case, also fulfilling criteria for definite acute generalized exanthematous pustulosis (AGEP), all probable and definite cases (n=117) were analyzed in this study (**Fig. 1**).

Demographics

As shown in **Table 1**, 97 were community cases, admitted because of the reaction, whereas in 20 cases the reaction started in hospital. An earlier cADR had been experienced by 22 patients, including one case with a prior episode of DRESS to the same drug. Females were predominant and significantly younger than males (p=0.03), especially in cases related to antiepileptics (median 37 vs. 47 years) and antibiotics (median 38 vs. 58 years), while no difference was observed for allopurinol (median 63 vs. 61 years). There was no patent difference by gender in indication for treatment. The most frequent co-morbidity was epilepsy (19.7%). We considered 16 patients (13.7%) to be immunocompromised: 1 by co-morbidity (HIV infection) and 15 by co-medication (systemic use of corticosteroids and/or other immunosuppressive/-modulating agents).

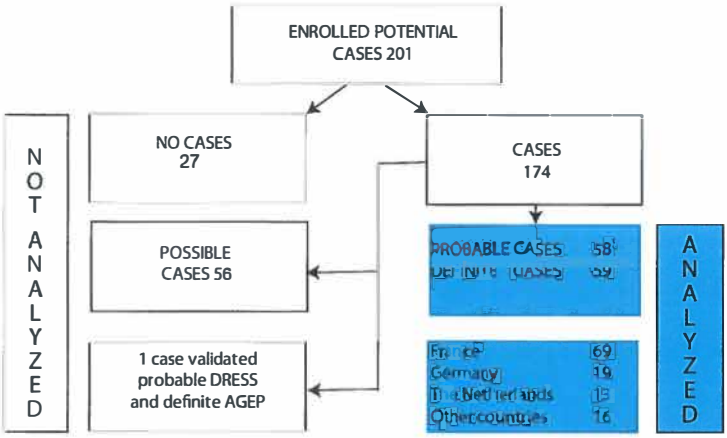

Figure 1. Flowchart of inclusion

Characteristics

As shown in **Table 2**, fever ≥38.5°C was documented in 90% (and fever 38.0°C-38.5°C in 7%); 21% experienced more than one episode of fever. Lymphadenopathy was observed in 54%.

Almost all cases (99%) showed one or more haematological abnormality. Eosinophilia, defined as an absolute eosinophil count ≥700/μL, was present in 95% and ≥1,500/μL in 81%. Atypical lymphocytes were observed in 68 cases (67%). Although no part of the validation score, we also noticed other haematological abnormalities. Leukocytosis (median 18,950/μL, interquartile range (IQR) 15,500-29,000/μL) was found in 95% and lymphocytosis in 48%. Neutrophilia (78%) was predominantly present in the early phase of the reaction, while monocytosis (67%) occurred later. Lymphopenia (5%, data not shown), thrombocytopenia (7%), and thrombocytosis (19%) were infrequent.

Table 1. Demographics, co-morbidities, concomitant medication

	DRESS n = 117		SJS/TEN* n = 379	
Demographics				
Sex, male/female ratio	0.77	(51/66)	0.62	(145/234)
Age all (median, interquartile range)	48	(30-62)	50	(28-68)
Age male (median, interquartile range)	57	(34-66)	47	(30-62)
Age female (median, interquartile range)	44	(29-59)	51	(28-72)
Community cases	97	(82.9%)	379	(100%)
Earlier cADR	22	(18.8%)	52	(13.7%)
Co-morbidities				
Convulsive disorders	23	(19.7%)	47	(12.4%)
Collagen vascular disease	10	(8.5%)	27	(7.1%)
Diabetes mellitus	14	(12.0%)	36	(9.5%)
Pre-existing kidney disorder	7	(6.0%)	30	(7.9%)
Pre-existing liver disorder	6	(5.1%)	26	(6.9%)
Recent cancer**	6	(5.1%)	40	(10.6%)
radiation therapy	1	(0.9%)	16	(4.2%)
HIV	1	(0.9%)	25	(6.6%)
Acute infections (4 wks before onset reaction)	25	(21.4%)	165	(43.5%)
Concomitant medication				
Immunosuppressive / -modulating agents***				
- corticosteroids ≤ 8 weeks / > 8 weeks	7/3	(8.5%)		14.8%
- other ≤ 8 weeks / >8 weeks	3/2	(4.3%)		

* EuroSCAR-study [32]

** Recent cancer: diagnosed during last 2 years before index date or, if diagnosed earlier, still treated

*** Not including colchicine, combined with allopurinol ≤8 weeks in 4 cases

Table 2. Characteristics of probable and definite cases of DRESS

	Total 117	
	number	Percentage*
Fever ≥ 38.5°C	103/114	90
Lymphadenopathy	61/112	54
Haematological abnormalities	113/114	99
- Eosinophilia	108/114	95
- grade 2 (≥ 1500/μL)	*92*	*81*
- grade 1 (700-1499/μL)	*16*	*14*
- Atypical lymphocytes	68/102	67
- Leukocytosis >10.000/μL	99/104	95
- Neutrophilia >7000/μL	81/104	78
- Lymphocytosis > 3000/μL	50/104	48
- Monocytosis > 1000/μL	47/70	67
- Thrombocytosis > 400.000/μL	20/104	19
- Thrombocytopenia < 100.000/μL	7/104	7
Skin**	117/117	100
- rash extent > 50%	79/104	76
- rash suggestive	68/104	65
- facial oedema	89/117	76
- monomorphic maculopapular	18/117	15
- polymorphous maculopapular	99/117	85
- urticarial	*12*	*10*
- exfoliative	*11*	*9*
- lichenoid	*4*	*3*
- pustules	*35*	*30*
- purpura	*31*	*26*
- infiltrated plaques	*27*	*23*
- blisters	*19*	*16*
- target-like lesions	*14*	*12*
- eczema-like lesions	*8*	*7*
- duration exanthema ≥ 15 days	51/117	44
Mucosal involvement	66/117	56
- mouth/throat/lips	*61*	*52*
- eyes	*15*	*13*
- genitalia	*8*	*7*
- other	*8*	*7*
Internal organ involvement	107/117	91
- 1 organ involved	42	36
- 2 organs involved	41	35
- > 2 organs involved	24	21
- liver	*86/114*	*75*
- kidney	*40/108*	*37*
- lung	*33/104*	*32*
- muscle/heart	*13/99*	*13*
- spleen	*12/79*	*15*
- pancreas	*3/77*	*4*
*- other****	*13/117*	*11*
Duration DRESS ≥ 15 days	107/109	98

* Denominator number of cases, investigated for the feature

** Available pictures 106 (91%) and biopsies 91 (78%)

*** Including gastro-intestinal tract (6) central nervous system (5), thyroid gland (2)

Figure 2. Skin reaction. A. Extensive erythematous maculopapular rash with indurated papules. B. Close-up of indurated papules on belly. C. Exfoliative dermatitis. D. Peri-orbital oedema, scaling, and residual facial erythema and pustules.

All patients experienced an acute skin eruption (**Fig. 2**). Extent and morphology however were only rated when photographs were available and informative (n=104). In 76% skin involvement exceeded 50% of the body surface area (BSA), while in 65% morphology fulfilled two or more criteria suggesting DRESS (see appendix). The rash concerned a monomorphic maculopapular, sometimes confluent and/or oedematous erythema in 15%, while in all other cases it was polymorphous, including additional varying combinations of other lesions such as pustules or tense blisters with, except for two cases, negligible detachment. Pruritus (81%) was more frequent than burning/pain (35%). Facial oedema was observed in 76%. Mild mucosal involvement was recorded in 56%; in 15% more than one mucosa was affected. Most frequent were oral lesions (52%), including lips (42%) oral cavity (40%), and throat (8%).

Two or more internal organs were involved in 56%, and one in 36%. Most frequently it concerned liver (75%), kidney (37%), and lung (32%). Kidney involvement was significantly more frequent in allopurinol than in carbamazepine related cases (60% vs. 17%, *p<0.01)*, whereas liver involvement did not differ significantly.

HHV6 (re)activation was demonstrated on serum samples in 20 of 56 routinely investigated cases in the active phase of the disease (36%) by PCR and/or positive IgM or a fourfold rise in IgG titre. EBV/CMV (re)activation was observed in 3 cases.

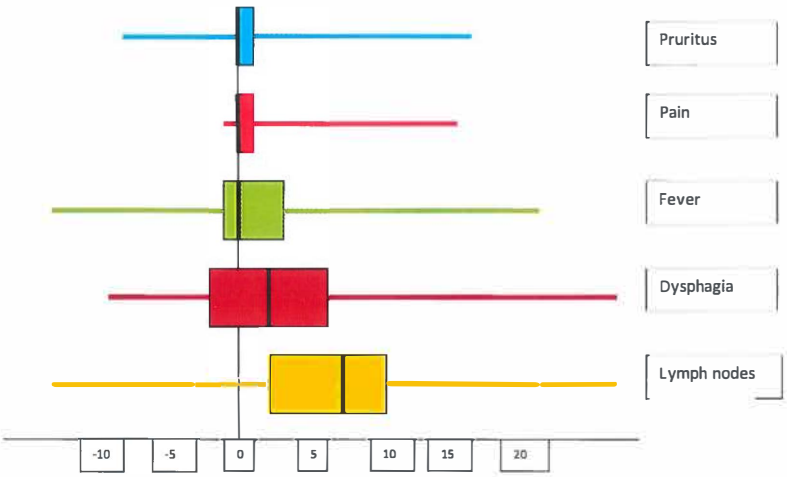

Figure 3. Latency prodromal symptoms (days)

Course and outcome

Some signs or symptoms such as pruritus, skin pain, fever, dysphagia and lymphadenopathy may appear before skin lesions (**Fig. 3**). In nearly half the cases the skin eruption persisted ≥15 days, while in all but two the full course of DRESS lasted ≥15 days. Mean in-hospital stay for community cases was 18.7 ± 11.5 days (median 17, IQR 11-23 days). During the acute phase, 2/117 patients died.

Culprit drugs

The results of the expert decision on drug causality are presented in **Table 3**. Overall 642 medicines (median 4, IQR 2-7 per patient), containing 316 different therapeutically active components, were used in the month before the probable index-day. The number of suspects was substantially reduced after elimination as a result of time relation. In 66 cases, only one (43) or two (23) drugs remained, most often including a single drug of high notoriety. All cases in which highly notorious drugs were eliminated because of long term use (allopurinol 61, 102, and 132 months, oxcarbazepine 11 months, and fluindione 408 months) were exposed to an alternative highly notorious drug within the chosen time window.

AED were considered responsible in 36%. Epilepsy was the most common indication for use of phenytoin or lamotrigine, while carbamazepine was prescribed for other indications, e.g. mood disorders or pain, in 65%. Only once an AED (phenytoin) was combined with dexamethasone for seizure prophylaxis in brain tumour. Allopurinol (18%), was prescribed for

Table 3. Culprit drugs and time relation of drugs taken within one month before the reaction

Exposure	cases	median	interquartile range
At least one drug	115 (98%)		
Total number of drugs used	642	4	2-7
Causality	**cases**	**drugs**	
Very probable	38 (32%)	38	
Probable	55 (47%)	58*	
Possible	10 (9%)		
undetermined	5 (4%)		
unlikely	9 (8%)		
Associated (very) probable drugs	**cases**	**median latency**	**interquartile range**
AED	43 (36%)		
- carbamazepine	*23*	*29*	*20-36*
- phenytoin	*8*	*29.5*	*26.5-37*
- lamotrigine	*8*	*26.5*	*20-34*
- oxcarbazepine	*2*	*n.a.*	*n.a.*
- phenobarbital	*2*	*n.a.*	*n.a.*
Allopurinol	21 (18%)	20	16.5-31
Sulphas	14 (12%)		
- sulfasalazine	*8*	*20*	*17.5-25*
- dapsone	*3*	*n.a.*	*n.a*
- sulfamethoxazole-trimethoprim	*2*	*n.a.*	*n.a*
- sulfadiazine	*1*	*n.a.*	*n.a.*
Antibiotics	13 (11%)		
- vancomycin	*7*	*17*	*13.5-20*
- minocyclin	*4*	*20*	*16.5-26*
- amoxicillin	*1*	*n.a.*	*n.a.*
- ampicillin/sulbactam	*1*	*n.a.*	*n.a.*
Other drugs**	5 (4%)	26	16-29.5

n.a.: not applicable

* Equally suspected high notorious drugs in the same case: allopurinol/fluindione, oxcarbazepine/ phenobarbital, and carbamazepine/phenytoin.

** Flavoxate, fluindione, nevirapine, phenylephedrine-acetaminophen, strontium ranelate.

gout in 6 and hyperuricemia in 15 cases, with a starting daily dose of 300 mg in 15, 200 mg in two, and 100 mg in four cases. Antimicrobial sulfonamides/dapsone (sulphas) were suspect in 12%, especially sulfasalazine and dapsone, other antibiotics in 11%, predominantly vancomycin and minocycline, and other drugs in 4%. In 9%, drugs of low notoriety were concomitantly used with drugs without notoriety, while another 4% was classified as undetermined, due to polypharmacy and absence of a notorious drug. No likely drug could be detected in 8%.

For all cases with a "very probable" or "probable" causality, median latency was 22 days (IQR 16-30 days) and mean latency 25.9 ± 19.1 days. Between the two most often appointed drugs, carbamazepine and allopurinol, latency differed significantly *($p<0.01$)* with a mean of 32.0 ± 16.7 days and 24.5 ± 13.6 days respectively.

Overlap with other types of SCAR

Of 118 probable/definite DRESS cases, 8 shared some features with SJS/TEN or AGEP and were re-reviewed for the alternative SCAR. Three cases (3%) were considered true overlap: one probable DRESS fulfilled the criteria of definite AGEP and was discarded from analysis in this study, one probable DRESS also validated as probable AGEP, and one definite DRESS as probable SJS/TEN, both were included as DRESS.

Discussion

Strengths and weaknesses of the study

This large prospective multinational study allows detailed analysis of clinical and biological features of DRESS and the relative contribution of "high risk" drugs. Since notification and enrolment of cases was independent of outcome, exposure to specific medication or other risk factors, we consider our results as likely less biased than those of most prior series.[15,16,24-29] Moreover, prospective collection of data through direct interviews of patients and treating physicians using a structured reaction-specific questionnaire, and validation by an expert committee using a standardized scoring system, clinical photographs, clinical and biological parameters contributes to the strength of the study. Our validation criteria and cut-off points are stricter than earlier case series including those which used RegiSCAR inclusion criteria as diagnostic criteria, resulting in less heterogeneity of cases (see Appendix).[16,23,29] Moreover, evaluation of case reports (of DRESS) is often not possible due to lacking transparency of data.[18] Combining a scoring system with an expert review, blinded for drug exposure and other risk factors, has proven to be effective for validationin SJS/TEN and AGEP.[30,31]

On the other hand, the nature of our study implies limitations to address adequately questions such as efficacy of treatment, late complications and sequelae. Cutaneous manifestations were part of our inclusion criteria, implicating that potential cases without overt skin lesions were

likely missed. However, a recent review of the literature indicated that almost all reported cases experienced a skin reaction.[18]

Not all physicians are familiar with DRESS, introducing risk of biased notification and absence of relevant laboratory investigations during the first days of the reaction, potentially resulting in underscoring of asymptomatic features. Moreover, recognition of the syndrome and complete collection of its symptomatic and asymptomatic features is often complicated. First symptoms may be seemingly harmless and each feature may be of variable onset and severity, leading to confusion and delay in diagnosis. Furthermore, features like eosinophilia and internal organ involvement tend to abate or disappear after treatment with systemic corticosteroids.

Several findings have been mentioned in previous reports and could be expected since they were part of our diagnostic score. However, the prospective and structured nature of our study enables a more detailed description of mucocutaneous involvement, and better assessment of the prodromal period, prevalence of key features such as eosinophilia and organ involvement, and distribution of inciting drugs.

Demographics

Contrary to most reports, our study showed slight female predominance (male/female ratio 0.77).[5,7,10,13,15,18,24,25] This predominance has also been reported for SJS/TEN (0.62), and AGEP (0.80) in a comparable population.[32,33] Striking and unreported hitherto, women were significantly younger than men, a difference not observed in SJS/TEN or AGEP (EuroSCAR, unpublished data). We do not have a satisfactory explanation for this finding.

As shown in **Table 1**, the frequency of prior rheumatic/collagen vascular disease was strikingly high (8.5%) as previously reported for SJS/TEN, while that of cancer (5.1% vs. 10.6%) was lower and close to the control group for SJS/TEN.[32] Our collection also included less HIV infected patients than observed in SJS/TEN or earlier reported in DRESS.[24,25,29,32] This may reflect a different or changing medication profile or that abacavir hypersensitivity does not sufficiently meet our criteria for DRESS (appendix).[23]

Contrary to SJS/TEN and earlier case series in DRESS, immunocompromised patients were not clearly overrepresented, and their profile did not significantly differ from that of other cases in our study (data not shown).[25,29,32] Related to the relative high prevalence of corticosteroid maintenance therapy in the context of brain tumour and co-medication with AED in SJS/TEN, exposure to corticosteroids was lower (8.5% vs. 14.8%).

Characteristics

High fever usually starts at the beginning of the reaction, and regularly precedes the eruption, generating concern for underlying infections.[1,4] A long lasting, polymorphous rash, and facial oedema are characteristic for DRESS. Facial oedema (76%) is more manifest than often stated.[4,15,16,25] Especially in combination with high fever and an eruption, it constitutes a warning

signal because in common cADR the face is usually spared. Mucosal involvement (56%), mainly of lips and oral cavity, was more frequent than generally assumed, however, contrary to SJS/TEN rather mild and less haemorrhagic.

Haematological abnormalities were far more frequent and diverse than usually described, reflecting that retrospectively collected cases are prone to missing informative biological data and underlining the importance of a full haemogram in DRESS. In our study, leukocytosis was common (95%) and often considerable. Transient eosinophilia (95%) was far more present than usually reported.[7,15,16,24,25,34] Hypereosinophilia >1500 cells/μL, if persistent, can be toxic to endothelial cells and contributes to organ damage such as interstitial nephritis, pneumonitis, myositis, eosinophilic carditis, pancreatitis, thyroiditis or encephalitis.[4,35,36] Remarkably, also neutrophilia (78%), and monocytosis (67%), usually not reported in DRESS, were frequent. Neutrophils, especially when activated, may also be implicated in tissue damage. Atypical lymphocytes, often regarded as characteristic for DRESS, were found in 67%, while lymphocytosis was observed in 48%. The pattern of leukocytosis, combined with neutrophilia in the early stage and monocytosis in a later stage is frequent in other strong inflammatory reactions; the combination with eosinophilia however is rather characteristic for DRESS. Thrombocytopenia/thrombocytosis, both occasionally reported, were quite infrequent.

Lymphadenopathy (54%) was observed more frequent than sometimes reported.[16,24,25,29] Visceral involvement often determines severity in DRESS. Liver involvement was frequent (75%), most often expressed by transiently disturbed liver function tests, although also hepatomegaly, sometimes with coagulopathy, was observed. In addition, we regularly noted participation of kidney (37%), ranging from mild proteinuria to severe renal function disturbances needing transient haemodialysis (data not shown), lung (32%), and more incidentally of muscle/heart, spleen, pancreas, gastrointestinal tract, central nervous system, and thyroid gland.

Reactivation of herpes viruses, especially HHV-6, often described in DRESS and even considered a criterion by Japanese experts, is held responsible for a more severe and/or protracted course.[5,7,19,21,34,37,38] HHV6 reactivation was observed in 20 of 56 of our cases (36%), routinely investigated by the treating physicians. This is less than in earlier, especially Asian series, where it reaches 60%.[7,21] This discrepancy might be explained by less elaborate investigations in our cases.

Course and outcome

For assessment of course, latency time and drug culpability, correct establishment of onset of the reaction is essential. The prodromal stage, defined as the period between onset of the reaction and start of the exanthema, lasted up to 2 weeks (median 1 day, IQR 0-4, range 0-14 days). Early signs and symptoms such as fever, lymphadenopathy, flu-like symptoms, sore throat/dysphagia, burning pain and pruritus can easily be overlooked or misdiagnosed. Incidentally, we also noticed asymptomatic organ or haematological involvement before the

onset of erythema. However, laboratory investigations or medical imaging will generally only be performed at a later stage, after admission or suspicion of DRESS. Notwithstanding our efforts on systematically collecting early signs and symptoms as these are crucial for determining the index date, we cannot exclude that these were sometimes missed, and that the onset of the disease was occasionally a few days earlier. This might partially contribute to the longer latency time in DRESS compared to other SCAR.

Mortality was considerably lower in the acute phase than usually reported, likely reflecting bias in published retrospective studies.

Culprit drugs

The process of determining drug causality was quite straightforward, and (very) probable causality was more frequent than in SJS/TEN (80% vs. 69%).[39] Selection of potential culprits, based on temporal relation but blinded for drug names, clearly pointed towards notorious suspects in the majority of cases. Noteworthy is the rather limited spectrum of causative drugs in DRESS, with carbamazepine as leading drug followed by allopurinol. Although lack of controls and validated rules for causality assessment could easily have led to spurious temporal associations of widely used drugs, these did not appear.

Although latency times exceeding 3 months have been reported, risk was mostly confined to medication started within 2 months. Cases in which highly notorious drugs were eliminated because of long-term use were all exposed to another highly notorious drug at a later date. Risk, confined to relative recently introduced exposure has also been reported for SJS/TEN and is of considerable relevance for long-term use of e.g. allopurinol or AED.[40] In addition, most cases using drugs without significant risk had been exposed to a highly notorious drug in parallel.

As could be expected, epilepsy (19.7%) was a frequent indication for AED in DRESS, although carbamazepine was used in 65% for other indications than epilepsy, reflecting increasing use for new indications. Allopurinol seems to have passed sulphas as frequent inducer of DRESS.[11] It concerned first use except for one case in which prior exposure also resulted in DRESS. Noteworthy was the significantly higher prevalence of renal involvement in cases related to allopurinol compared with carbamazepine, whereas earlier reported differences in liver involvement were not found.[15,24,41] Allopurinol is increasingly prescribed, also without clear indication and in high doses; 17/21 patients started allopurinol with a daily dose of ≥200 mg. Daily doses equal to or exceeding 200 mg were also associated with a higher risk for SJS/TEN.[42]

The prodromal stage and the quite prolonged latency time in DRESS introduces risk of protopathic bias, especially for antibiotics and NSAIDs, necessitating scrutinous investigation of the prodromal stage. Of interest is the variation in drug-specific latency time. The difference between carbamazepine (median 29 days) and allopurinol (median 20 days) was significant *($p<0.01$)*.This difference in dynamics of the reaction suggests a drug-specific pathomechanism, which has to be further elucidated. Also remarkable are different latency times between some

earlier series and our findings.[7,15,16,24] Responsible could be a less strict case definition, leading to a more heterogeneous study population, retrospective assessment or incomplete collection of data, different drug profiles, and underestimation of the prodromal period.

Overlap

SJS/TEN and AGEP can share some features of internal involvement with DRESS, although to a milder and more limited extent.[43] Mucocutaneous features however, are quite discriminative in all three types of SCAR. Blisters, occasionally present in DRESS, are generally tense and related to dermal oedema.[4] Mucosal involvement differs from SJS/TEN in being rather mild. Compared to AGEP, flexural accentuation is lacking, while pustules, if present, are follicular and mainly limited to the face and upper thorax. Striking is also the subacute character and protracted course in DRESS, while particularly AGEP is characterized by an acute onset and quick resolution. Histopathology of DRESS is quite distinct from that of TEN and AGEP and lacks full thickness necrosis or sterile nonfollicular subcorneal pustules.[44,45] Applying the RegiSCAR validation score systems for SJS/TEN and AGEP to cases, validated probable or definite DRESS, resulted in negligible overlap.[23,30,31] This supports that DRESS is an original phenotype and confirms a reliable performance of our scoring systems.

There is a remarkable overlap of several major culprit drugs in DRESS and SJS/TEN, such as allopurinol, carbamazepine, phenytoin, lamotrigine, and sulfasalazine. In a comparable population, overall latency in SJS/TEN and AGEP were shorter than in DRESS.[32,33] Compared to SJS/TEN or AGEP, latency is prolonged and the prodromal period is more variable and extended in DRESS. Comparing latency in DRESS and SJS/TEN for the two most prevalent drugs in our study, we noticed a significant difference for carbamazepine (median 29 days versus 15 days, (**Fig. 2**) while for allopurinol (median 20 days versus 19 days) differences were less obvious (EuroSCAR unpublished data).

On the other hand, AED and allopurinol, important culprits both in SJS/TEN and DRESS, constitute no clear risk in AGEP. Quinolones and aminopenicillins, important triggers for both SJS/TEN and AGEP, are not clearly associated with DRESS, while vancomycin and minocycline, less prominent in other SCAR, are regularly implicated in DRESS. Co-trimoxazole and oxicam NSAIDs, showing a strong association with SJS/TEN, seem less a risk factor in DRESS.[7,15,25,32,46]

Conclusion

Our validation scoring system for DRESS, based on clinical and biological parameters and exclusion of other entities, resulted in only minor overlap with other SCAR. Clinical and biological characteristics, causative drugs, and time relation support that DRESS is an original phenotype among the spectrum of ADRs.

DRESS is a serious and multiorgan ADR, exhibiting variable combinations of features. Because cutaneous symptoms are generally present and often the first and most visible manifestation, the syndrome is classified as a SCAR. However, potentially severe involvement of visceral organs makes this syndrome of interest for all physicians.

Awareness of DRESS is a prerequisite for diagnosis, since it is a syndrome in which signs and symptoms often evolve sequentially. This introduces risk of delayed diagnosis and separate treatment of each symptom. In particular high and spiking fever and haematologic abnormalities may raise suspicion of an infection. Early recognition, followed by prompt withdrawal of the culprit drug is the most decisive step to avoid disease progression and restore health.

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APPENDIX

DRESS validation score

SCORE	-1	0	1	2	min	max
Fever ≥ 38.5 ° C	No/U	Yes			-1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia		No/U			0	2
Eosinophils			700-1499/µl	≥1500/µl		
Eosinophils, if leukocytes <4000			10-19.9%	≥20%		
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement					-2	2
Skin rash extent (% BSA)		No/U	>50%			
Skin rash suggesting DRESS	No	U	Yes			
Biopsy suggesting DRESS	No	Yes/U				
Organ involvement *					0	2
Liver		No/U	Yes			
Kidney		No/U	Yes			
Lung		No/U	Yes			
Muscle/heart		No/U	Yes			
Pancreas		No/U	Yes			
Other organ(s)		No/U	Yes			
Resolution ≥ 15 days	No/U	Yes			-1	0
Evaluation other potential causes: ANA Blood culture Serology for HVA/ HVB/ HVC Chlamydia-/ Mycoplasma pneumoniae Other serology/PCR If none positive and ≥ 3 of above negative			Yes		0	1
TOTAL SCORE					-4	9

U = unknown/unclassifiable

* After exclusion of other explanations: 1 = 1 organ, 2 = ≥ 2 organs

Final score <2: No case
Final score 2-3: Possible case
Final score 4-5: Probable case
Final score >5: Definite case

Fever (-1, 0)
If core temperature is < 38.5°C: deduction of 1 point

Lymphadenopathy (0, +1)
Tender enlarged lymph nodes at least at two different anatomic locations: > 1 cm. 1 point

Peripheral blood:
Eosinophilia: (0, +1,+2)
-Absolute eosinophilia of 700-1500 10^9E/l:1 point, if ≥ 1500 10^9E/l: 2 points
- If leukocyte count is < 4000 10^9E/l: % eosinophils ≥10%-20%: 1 point, eosinophils ≥ 20%: 2 points
Atypical lymphocytes: *(0, +1)*
If present: 1 point

Skin reaction *(morphology, extent)* ***(-2, -1, 0,+1, +2)***
a. Morphology (-1, 0, +1): If morphology is suggestive for DRESS: 1 point; if suggestive for a different type of reaction: deduction of 1 point, otherwise 0 points.
Morphology is considered suggestive for DRESS at presence of ≥ 2 of following criteria:
- scaling/desquamation e.g. exfoliative dermatitis
- oedema, especially facial oedema (excluding lower leg oedema)
- purpura (excluding lower leg)
- induration
b. Extent rash (0, +1) If morphology is compatible with DRESS and extent rash > 50% body surface area (BSA): 1 point
c. Histology (-1, 0): When histology is compatible with DRESS: 0 points, when suggestive for another diagnosis: deduction 1 point;

Involvement internal organs: (0, 1, 2) For acute involvement of each organ, 1 point is given, with a maximum of 2 points. Organ involvement is based on history, clinical investigation, medical imaging, biopsy or other tissue/fluid investigation. Organ involvement is also calculated at presence of the following abnormal laboratory values:

***Liver* (0, 1)**

- ALAT > 2 times upper normal limit (*UNL) on at least 2 successive dates **or**
- conjugated bilirubin >2* UNL on at least 2 successive dates **or**
- ASAT, total bilirubin, alkaline phosphatase (AP) all >2* UNL at least

***Kidney* (0, 1)**

Serum creatinine more than 1.5 times above the base value for the patient on at least 2 successive dates, and/or proteinuria above 1g/day, haematuria, decreased creatinine clearance, decreased GFR

***Lungs* (0, 1)**

Cough and/or dyspnoea in conjunction with

- evidence of interstitial involvement on imaging and/or
- abnormal broncho-alveolar lavage fluid, or biopsy and/or
- abnormal blood gasses

***Muscle, heart* (0, 1)**

Muscle pain and/or weakness, myocarditis (often nonspecific symptoms: hypotension, fatigue, chest pain, dyspnoea, malaise, palpitations, tachycardia, cardiac dysfunction, cardiomegaly, sudden cardiac death), with

- Raised serum creatine phosphokinase (CPK) > 2*UNL
- Raised isoenzymes: CPK-3/CPK-MM (indicative for skeletal muscle), raised CPK-2/MB fraction (indicative for heart muscle involvement).
- Serum troponin T > 0.01 µg per liter
- Abnormal imaging: chest X-ray/ECHO/CT/MRI/EMG including ECG: ST-T electrocardiogram abnormalities or conduction defects (ST-segment depression, T-wave inversions or non-diagnostic ECG changes (paced or bundle branch block)).

Endomyocardial biopsy .

***Pancreas* (0, 1)**

Amylase and/or lipase ≥ 2*UNL

Other organs: spleen, thyroid gland, central nervous system, gastrointestinal tract

- Clinical symptoms and additional investigations: enlargement/imaging, including EEG
- Abnormal lab values: TSH, FT4, FT3.
- Biopsy

Duration (-1, 0)

If the total duration of the reaction is ≤ 15 days or unknown: deduction 1 point

Exclusion of other causes, e.g. infections, virus (re)activation (0, 1)

- *Hepatitis A/B/C*
- *Mycoplasma- /Chlamydia pneumoniae*
- *Blood cultures ≤ 3 days of index date*
- *Other (infections): serology, PCR, microbiological cultures*
- *ANA*

In case of a positive result for any of these, organ involvement is re-evaluated for a possible alternative cause. If ≥ 3 mentioned groups are investigated and no positive result is found, an extra point is given to express thorough investigation for alternative causes.

EBV/CMV and HHV6/7 are also recorded; results however do not influence the score.

11

Flare-up of patch test of trimethoprim-sulfamethoxazole (co-trimoxazole) during oral desensitization.

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Summary

We report a flare-up reaction on earlier patch test sites of trimethoprim–sulfamethoxazole (co-trimoxazole) during oral desensitization with this drug. Similar local flare-up reactions have been described in contact dermatitis, but to the best of our knowledge, they have not yet been reported for systemically administered drugs.

Case report

A 36-year-old HIV-positive male developed an itchy maculopapular rash with fever (>39°C), 11 days after starting trimethoprim–sulfamethoxazole 960 mg daily for pneumocystis carinii pneumonia prophylaxis (CD4 lymphocyte count 74 × 10^9/l). At the time of the rash, and in the weeks before, he had not used any other medication. Trimethoprim–sulfamethoxazole was replaced by pentamidine inhalations, and the rash and fever disappeared within a week.

Two months later, highly active antiretroviral therapy (HAART) was started with good response and without complications. One year later, the patient was referred for evaluation of the reaction.

The patient had never used trimethoprim–sulfamethoxazole prior to the above. Two months before the rash started, he applied topical silver sulfadiazine without adverse effects. Patch testing with trimethoprim–sulfamethoxazole 10% (pure substance) and 30% (commercial preparation) in pet. resulted in a doubtful positive reaction; silver sulfadiazine cream 10 mg/ml and the European baseline series were negative.

One week later, retesting trimethoprim–sulfamethoxazole in duplicate on two different sites gave negative results. Subsequent in-patient oral desensitization with trimethoprim–sulfamethoxazole was attempted (**Table 1**). On D3, a few hours after the last desensitization step at a dose of 480 mg, he developed fever (38.3°C), a non-itchy flare-up of all six previous trimethoprim–sulfamethoxazole patch test sites, and a slightly increased CRP (18 mg/l, normal <5 mg/l) and eosinophilia (6.7%, normal <3%). On continuation of the therapeutic dose of trimethoprim–sulfamethoxazole (480 mg/day with a CD4 lymphocyte count between 100–200 × 10^9/l), the fever and the flare-up reactions disappeared within 1 week.

Table 1. Desensitization schedule

Day 1, suspension trimethoprim–sulfamethoxazole 48 mg/ml, diluted 1:10	
9.00 hours	1 ml
11.00 hours	2 ml
13.00 hours	5 ml
17.00 hours	10 ml
Day 2, suspension trimethoprim–sulfamethoxazole 48 mg/ml, undiluted	
9.00 hours	2 ml
15.00 hours	4 ml
21.00 hours	5 ml
Day 3, tablet trimethoprim–sulfamethoxazole 480 mg	
9.00 hours	1 tablet

Discussion

Opportunistic infections, such as pneumocystis carinii pneumonia, constitute a major problem in patients with HIV/AIDS for which sulfonamides like trimethoprim–sulfamethoxazole are the first choice for treatment and prophylaxis. Unfortunately, HIV/AIDS patients also have an increased risk of cutaneous adverse drug reactions to trimethoprim–sulfamethoxazole.[1,2] These are often due to a type 4 delayed-type hypersensitivity reaction, presenting with a maculopapular rash and fever, 7–14 days after initiation of the drug, although severe cutaneous adverse drug reactions like Stevens–Johnson syndrome/toxic epidermal necrolysis or a drug-induced multi-organ syndrome (DRESS) may develop.[3,4]

In HIV and AIDS, a shift from Th1 to Th2 cytokine profile can be observed; during HAART, this shift may be partly reversed. Adverse drug reactions related to Th2 cytokines thus could be expected (e.g. urticaria and anaphylaxis). Somewhat unexpectedly, many HIV-infected patients also show delayed-type hypersensitivity reactions (e.g. maculopapular rash and DRESS). The relative preponderance of CD8 cells over CD4 cells in HIV and AIDS could be relevant because CD8 cells have been implied as effector cells in some drug reactions.[5] In the abacavir hypersensitivity syndrome, a direct role for human leucocyte antigen-B*5701-restricted CD8+T cells was shown.[6] Although delayed-type hypersensitivity reactions are mainly Th1 driven, Th2 and regulatory cytokines are also involved in these reactions.[7] We assume that the generally increased risk of adverse drug reactions in these patients could be related to changes in regulatory T cells and cytokines. Initial studies indeed showed functional deficiencies in spite of increased numbers of regulatory T cells with progressive disease; recent studies, however, have not confirmed these observations.[8] Thus, the immunological basis of the increased rate of adverse drug reactions in HIV and AIDS is not yet fully understood. Moreover, (subclinical) viral infections and drug interactions may further complicate the analysis of such events.

Possible solutions when a reaction has occurred include continuation of treatment with antihistamines and steroids, a switch to an alternative drug or to stop and restart through desensitization or full dose. Although not yet fully proven, desensitization appears to result in fewer treatment discontinuations and adverse reactions compared with a stop and restart at full dose.[1,2] Generally, patch tests are regarded safe for determining the culprit in cutaneous adverse drug reactions, and they are positive in 32–50%.[9]

In contact dermatitis, flare-up reactions of earlier patch test sites have been described for nickel and gold after systemic provocation.[10,11] To the best of our knowledge, these reactions have not been reported in cutaneous adverse drug reactions.

In allergic contact dermatitis, resident CD4+CCR10+ T cells can still be detected in clinically normal skin on patch test sites 3 weeks after testing.[12] Persistent local CD4+CCR10+ T cells may possibly be triggered by later allergen ingestion, resulting in a flare-up. Moreover, in flare-ups

of nickel patch tests, activation of local memory function seems to be inversely related to the period until reactivation.[10]

In our case, all six sites earlier tested with trimethoprim–sulfamethoxazole showed a clear flare-up reaction at provocation, possibly reflecting the presence of local memory in the skin. Restriction of the clinical reaction to earlier tested skin could be explained by the long interval between the original reaction and desensitization, compared with the short interval between patch testing and desensitization.

Conclusion

We report a flare-up of previous patch test sites after oral desensitization with trimethoprim–sulfamethoxazole, suggesting persistent local memory after patch testing.

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12

Summary of the chapters/ Samenvatting van de hoofdstukken

Summary of the chapters

Safety, efficacy and quality of drugs are issues of all ages. Adverse drug reactions (ADR), inevitable consequence of drug therapy, are amongst the most important causes of iatrogenic illness in terms of morbidity and mortality, and are as old as medicine itself. Particularly in the last decades, a more variable array of new drugs, e.g. targeted drugs and biologicals, have been introduced, resulting in prolonged life expectancy and better quality of life. On the other hand, a significantly increased frequency, quantity, and diversity of drug-intake contribute to more frequent and heterogeneous ADR. The incidence of ADR is high and not expected to decrease in future, due to an increasing life expectancy, partially facilitated by medicines and addition of targeted and immune modulating drugs to the vast array of drugs. Polypharmacy, a change in metabolism and a decreasing function of organs in the elderly are risk factors for ADR, and prevention and management of ADR constitute an important issue for healthy aging and quality of life in the elderly. Moreover, the potency of new drugs for causing ADR often only becomes clear after their introduction to the market: on the one hand because of the relative rarity of ADR compared to the rather limited number of persons participating in premarketing trials, on the other hand because premarketing testing is preferably performed in healthy young males, while frail patient groups such as babies, pregnant and fertile women, the elderly, and people with pre-existing diseases are excluded from testing.

Dermatologists regularly see patients who are supposed to have a (muco)cutaneous ADR (cADR). Virtually all drugs can provoke cADR, although each drug by itself is generally only rarely responsible. The incidence of cADR rather reflects the vast use of medicines than their individual reactivity. In addition, cADR can present a wide range of distinct pictures with a multitude of clinical and biological features, which regularly show resemblance or some overlap with other diseases, including idiopathic dermatoses. Also, the variety of cADR is probably based on various pathomechanisms, most of which are still largely unknown. Moreover, it is often difficult to assign a single drug as the culprit, particularly in cases of polypharmacy. The huge clinical variability and heterogeneity, and resemblance with many other conditions can easily result in misdiagnosis. Both under- and over-diagnosis are important issues, especially in cases with hypersensitivity reactions. Misclassification as drug allergy has consequences for future treatment choices and may result in the use of more expensive and/or less effective treatment modalities, while under- diagnosis may result in a potentially more severe reaction at future re-administration of the drug.

Awareness of cADR is a prerequisite for proper diagnosis, and identification of the reaction type and the causative drug can be quite challenging. Similar to idiopathic dermatoses, case definition of the various types of cADR is mainly based on the morphology and distribution of the (muco)cutaneous lesions. A clear case definition can help to recognize clinical patterns and establish diagnosis, treatment, and prognosis in cADR. Fortunately, most cADR are mild and transient and apart from supportive treatment, early recognition followed by prompt withdrawal

of the culprit drug is most often sufficient to avoid progressive development and restore health. In some types of severe cutaneous adverse reactions (SCAR), however, also specific therapeutic intervention seems to be warranted to inhibit the cascade of immunological and non-immunological processes, elicited by the adverse reaction. This thesis explores various aspects of case definition, differential diagnosis, and treatment modalities of cADR and SCAR, with a focus on Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS).

Chapter 1 gives a general introduction to cADR and more specifically on a limited number of SCAR: SJS/TEN, AGEP, and DRESS, highlighting classification, case definition, and current understanding of pathogenesis and treatment.

The diversity of cADR is nearly infinite. However, it makes sense to distinguish entities rather than to consider all as a continuum, if it helps in finding original clinical patterns, with different courses, mechanisms, causes, prognosis and/or treatment modalities. SCAR and some of the other cADR are not necessarily restricted to the skin.

Often a skin reaction reflects a more general involvement of the body. Perhaps the most appealing example is DRESS, a multi-organ syndrome, in which besides a skin reaction, also lymphadenopathy, haematological abnormalities and visceral organ involvement can occur. Other SCAR such as SJS/TEN and AGEP can also display visceral involvement, although most often to a more limited degree, and differences in (muco)cutaneous features, combined with separate assessment of the extent and/or type of involvement of other organs, will generally assist in establishing diagnosis.

In **chapter 2** the controversy regarding the treatment of SJS/TEN with corticosteroids is addressed. Aim of this retrospective study in a small, uncontrolled series of twelve consecutively hospitalised patients with a validated diagnosis of SJS/TEN was to evaluate the efficacy of dexamethasone pulse therapy.

Besides multi organ failure, infections are the major cause of mortality in SJS/TEN. Historically, corticosteroids were advocated for treatment, but since the mid-1980s the use of corticosteroids in SJS/TEN became controversial and was considered detrimental by some authors as a reaction to some reports with a negative outcome. Subsequently, therapeutic intervention with other agents such as thalidomide, intravenous immunoglobulin (IVIG) or ciclosporin has been proposed, but good evidence that, in addition to optimal supportive therapy, specific drug treatment is beneficial in SJS/TEN is still lacking. A double blind randomized controlled study with thalidomide had to be stopped due to increased mortality, at hindsight in the active treatment arm. Results of uncontrolled case series, treated with IVIG are contradictory and and provide insufficient evidence for promoting IVIG as standard treatment in SJS/TEN. Recently,

although not statistically significant, favourable outcomes have been reported in an open trial with ciclosporin.

Although the precise action of corticosteroids is still not well understood, corticosteroids are thought to have pleomorphic immunomodulating effects, probably probably through the inhibition of various cytokines. We believe that these drugs have ambiguous effects on SJS/TEN. If started too late and used for too long in too low a dose, their immunosuppressive effects may promote infections, and possibly delay wound healing. On the other hand, short courses of high-dose corticosteroids in early SJS/TEN have a good rationale, since they might inhibit immune mechanisms, also responsible for the cascade of events leading to apoptosis. High dose corticoids, given immediately after onset of SJS/TEN, may moderate the disease process by weakening the cytokine storm and reducing the excessive apoptosis that leads to full-thickness necrosis and extensive epidermal loss.

In our study, high dose therapy with dexamethasone (1.5 mg/ kg body weight/ day) was given as an intravenous pulse on three consecutive days, starting immediately after establishing the diagnosis of SJS/TEN. The study supported that short-term dexamethasone pulse therapy, given at an early stage of the disease, may contribute to a reduced mortality rate in SJS/TEN without increasing healing time.

Recent reports tend to be less negative towards corticosteroids, and seem to suggest that a larger multinational study on the effect of short courses of high dose corticosteroids in SJS/TEN is warranted.

Chapter 3 presents a retrospective analysis of patients with SJS/TEN and a history of lupus erythematosus (LE). The data were extracted from a large population based national registry of patients with a validated diagnosis of SJS/TEN. In addition, a review of the literature is given on this topic. The main purpose of this study was to evaluate differential diagnostic features for SJS/TEN and bullous manifestations in LE, clinically as well as histopathologically. A secondary aim was to evaluate the prevalence of LE in this group of patients with SJS/TEN.

Among 1366 patients with SJS/TEN in the study period (1990 to 2006), 17 with a sufficiently documented history of LE and available representative histologic material could be identified. In nine of these, no clinical or histopathological features of LE could be found shortly before or during the episode with SJS/TEN. The other eight patients, however, showed clinically and/or histopathologically some LE-characteristic features interfering with the diagnosis of SJS/TEN. A distinction could be made on clinical and histopathologic grounds: four patients were classified as SJS/TEN with a preceding LE exacerbation, and/or LE-typical histopathological features, and four as "TEN-like" LE.

SJS/TEN can occur in patients with LE and bullous manifestations in LE need not necessarily be interpreted as manifestation of LE. Most patients with SJS/TEN and a history of LE show clinical and histopathologic properties allowing clear differentiation. Occasionally however, acute cutaneous manifestations of LE and SJS/TEN can be phenotypically similar, caused by

extensive epidermal apoptosis. In these cases, especially history and clinical course may assist in their differentiation. Although no feature by itself is conclusive, a combination of recent LE exacerbation, evident photo-distribution, annular lesions and absent palmoplantar lesions and/or absent or only mild focal erosive mucosal involvement may favour LE over SJS/TEN clinically, while histopathologically particularly junctional vacuolar alterations combined with moderate to dense peri-adnexal and (deep) perivascular lymphocytic infiltrates point at a LE-related origin.

The relative high proportion of patients with a history of LE amongst the patients with SJS/TEN suggests a correlation between both, either LE being a risk factor for SJS/TEN or both sharing a mutual risk factor.

Chapter 4 presents the first systematic description of the histopathological spectrum of AGEP, based on a large series of cases, derived from two prospective multinational studies. All included cases were validated as probable or definite AGEP, according to a generally accepted validation score. Previous knowledge on the histopathology of AGEP mainly relied upon case reports and a few small clinical series. AGEP presents a rare, generally drug-induced reaction pattern, for which a range of differential diagnoses may apply. Key histopathological features in AGEP are superficial spongiform pustules, exocytosis of neutrophils, necrotic keratinocytes, papillary oedema, mixed dermal infiltrates, including (lower) middermal and interstitial infiltrates, containing neutrophils and eosinophils, and the paucity of classical plaque-type psoriatic epidermal changes. The diagnosis of AGEP can be based on these key histopathological features combined with clinical signs in favour of AGEP. These include an abrupt onset, short duration (≤ 15 days), association with recently introduced drugs, spontaneous resolution after withdrawal of the culprit drugs, and a non-recurrent tendency. The study also supports the concept that AGEP is a separate entity, which can also occur in patients with psoriasis. Interestingly, it was noticed that AGEP was more common in patients with a history of psoriasis than could be expected from the general population.

Chapter 5 presents a comparative study on the spectrum of histopathological features in patients with either probable or definite AGEP or with generalized pustular psoriasis (GPP). Differentiating AGEP from GPP, especially the acute "von Zumbusch" type, presents a clinical and histopathological challenge. Step sections of paraffin-embedded tissue, stained with hematoxylin-eosin, of both AGEP and GPP were systematically evaluated according to identical parameters and grades of severity. Whereas no single histopathological feature is diagnostic on its own, the combination of features and their grade of severity can substantially contribute to differentiate diagnosis. Features pointing at AGEP instead of the acute phase of GPP are the presence of eosinophils in the pustules or dermis, necrotic keratinocytes, mixed neutrophil-rich interstitial and (lower) middermal infiltrates, and absence of tortuous, dilated blood vessels. Moreover, chronic GPP demonstrated significant epidermal psoriasiform changes. In both acute and chronic GPP, dilated and tortuous superficial vessels were often found. These key

histopathological features, combined with the clinicopathological correlation, can assist in the distinction between AGEP and GPP in most cases. This study also supported that AGEP is not a variant of pustular psoriasis, but represents a separate entity. It also substantiated that AGEP is more often observed in patients with a history of psoriasis than could be expected from the general population.

In **chapters 6a and 6b** two cases of AGEP, induced by morphine are described. Morphine has a relatively safe profile regarding cADR, and has not previously been incriminated in eliciting AGEP.

Morphine is regularly administered post-operatively in short courses, but also for longer periods for the relief of severe chronic pain. Especially in the post-operative period, symptoms of fever, erythema and pustules can easily be erroneously ascribed to other factors such as infection, as in the first case; besides, the sometimes very small pinpoint pustules may easily be overlooked. Because AGEP is self-limiting and heals quickly after cessation of the culprit, the reaction can go unrecognised as drug related after a short course of drug therapy. After resolution of the reaction, morphine hydrochlorid was confirmed as the culprit by positive results of patch tests and a lymphocyte transformation test. Subsequently we observed a second case where morphine sulphate, amongst other drugs, was given in the setting of severe back pain. Complicating in this case, presenting with a TEN-like appearance, was a history of psoriasis, and a possible earlier SCAR, necessitating differentiation from GPP and TEN. Histology, however, was fairly discriminative in showing spongiform subcorneal pustules and mixed perivascular and interstitial dermal infiltrates, compatible with AGEP, as was the quick healing without recurrences after morphine was withdrawn. Morphine could be identified as the culprit through positive patch test results. Both cases demonstrate the importance of awareness of a cADR, especially when seemingly unexplainable symptoms occur, even when a drug has not previously been incriminated in the literature. Positive in vitro and/or in vivo tests, as reported, can be helpful in establishing a drug related aetiology and point at the specific offending medication. Of note is that the pustular patch test reaction nicely mirrored the original reaction of AGEP in the second case. Positive test results also support that AGEP is a delayed type hypersensitivity reaction, in which in addition to neutrophils also T-cells are involved.

In **chapter 7,** two patients are presented with symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), previously also known as the "baboon syndrome". The reaction was in both cases induced by omeprazole, a potent, widely used and well tolerated proton pump inhibitor, which has not earlier been explicitly associated with SDRIFE. Diagnostic criteria for SDRIFE are systemic drug exposure, sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area, involvement of at least one other intertriginous/flexural fold in a symmetrical distribution, and absence of systemic symptoms and signs. Although distribution and characteristics of the lesions in both patients were typical

for SDRIFE, our cases also showed some rather unusual features such as pustules, concomitant participation of other skin creases, minor systemic symptoms and signs, including mild relative neutrophilia and eosinophilia, and a longer latency time after start of the inciting drug than generally reported. Apart from localisation in the flexures, the presence of pustules, a wider distribution of lesions than commonly reported for SDRIFE, and mild systemic symptoms necessitated differentiation from AGEP.

In **chapter 8,** two patients are described who, after treatment with erlotinib (Tarceva®) for non-small-cell lung cancer, developed long-lasting widespread acneiform eruptions and xerosis cutis, probably rendering them susceptible to infection, resulting in extensive and disabling impetiginisation. Because both patients experienced a widespread itching pustular rash with accentuation of the lesions in the flexures, accompanied by fever in one patient, AGEP was considered.

Erlotinib is an epidermal growth factor receptor (EGFR) inhibitor, a member of a new group of molecularly targeted drugs that combines high efficacy against tumours with less and often self-limiting toxicity, as compared with traditional chemotherapeutics. Targeted agents are increasingly used for the treatment of cancer, especially in case of resistance to conventional antineoplastic drugs. Drawback is the frequent occurrence of adverse mucocutaneous reactions, resulting in substantial discomfort and morbidity. Besides, apart from well known cADR, these drugs may introduce several unfamiliar reactions, quite different from conventional medication.

Acneiform eruptions, caused by erlotinib, are based on the pharmacological properties of the drug, are class specific and dose related, and can be qualified as a type A reaction. Since acneiform eruptions more often occur in connection with a good therapeutic response, a proactive policy and good knowledge are important in the management of patients. Early and timely dermatological intervention may diminish the severity of this side effect, enable continuation of therapy and improve quality of life. Although the mechanism underlying this rash is not fully understood, probably an imbalance in the differentiation and maturation is involved, causing secondary inflammation. This may lead to a thinned stratum corneum and inflammatory infiltration of the follicles, which often become dilated and plugged by excessive keratin, occasionally promoting extensive secondary infection.

Chapter 9 addresses the issue of case definition and features of DRESS. These have been proposed, based on a review of the literature, pilotstudies, and consensus meetings of a multidisciplinary group of experts, mainly originating from Europe.

Already in 1950, both Welton and Chaiken *et al.* independently reported a case with a pronounced cutaneous and visceral reaction to phenobarbital respectively phenytoin (Dilantin®), both structurally related drugs. Subsequently a syndrome defined by "a triad of fever, skin rash and internal involvement" has been reported for the same and several other medicines under a wide variety of names, either related to the drug (anticonvulsant hypersensitivity syndrome),

to the organ most involved or the disease mimicked (mononucleosis-like syndrome) or the supposedly involved pathomechanisms (drug induced hypersensitivity syndrome or HSS). However, the term hypersensitivity for the reaction is rather unspecific and prone to confusion. It has led to the qualification as HSS of some cases of SJS/TEN and AGEP and even of some cases of more common cADR with one or more systemic signs or symptoms. It also introduced qualification of SJS/TEN as a variant of HSS and reports on overlapping entities. Since the word hypersensitivity is rather uninformative and ambiguous, the more informative and clinically relevant acronym DRESS is gaining use. In order to obtain a multinational homogenous cohort of patients for further study of DRESS, while a clear case definition was lacking, a diagnostic score was developed for validation of potential cases of DRESS as definite, probable, possible, or no case. A clear trend has been noticed that this new case definition is gaining general acceptance and is regularly referred to in literature nowadays.

Chapter 10 presents the description and analysis of a first prospective multicenter study of 117 cases validated as definite or probable cases of DRESS according to the newly developed validation score. In addition it also gives an overview of the clinical criteria and cut-off points of abnormal biological and laboratory findings for considering signs and symptoms as being DRESS-related.

Since notification and enrolment of cases were independent of outcome and exposure to specific medication or other risk factors, the results of this study are considered as likely less biased than those of prior retrospective series. Moreover, collection of data by trained interviewers through direct interviews of patients and treating physicians using a reactionspecific questionnaire, followed by a structured validation by an expert team according to the newly developed validation system using clinical photographs, structured data on course, clinical and biological parameters, and histopathology, but blinded for risk factors, contributes to the strength of the study. At validation, findings that could potentially be attributed to an alternative cause were excluded from attribution to the score. Besides confirmation of the rather variable character of DRESS with various combinations and severity of signs and symptoms, a delayed onset, and protracted course, original findings were female predominance, significant younger age of females, high prevalence of rather mild mucosal symptoms, frequent eosinophilia and atypical lymphocytes, and lower mortality than generally stated. In addition, a description was given of the prodromal symptoms that arise before mucocutaneous symptoms are noticed. The spectrum of inciting drugs was rather limited, with aromatic antiepileptics and allopurinol as the main culprits. Reassuring was that the newly developed validation score system resulted in only minor overlap with SJS/TEN and AGEP. The findings confirm that DRESS is an original phenotype among SCAR in terms of clinical and biological characteristics, causative drugs, time relation, and course.

Chapter 11 presents an interesting observation during a desensitisation procedure with trimethoprim-sulfamethoxazole (co-trimoxazole), because of an earlier severe cutaneous adverse drug reaction in a HIV-positive patient. About one year after the original reaction, two successive series of patch tests with cotrimoxazole were evaluated as weakly positive, respectively negative. Shortly thereafter desensitisation was performed. A few hours after the last desensitisation step (day 3) the patient developed erythema, confined to the sites of the previous patch tests, combined with transient fever, malaise, elevated C reactive protein and peripheral eosinophilia. The phenomenon of flaring of earlier patch tests has been described previously for nickel and gold after systemic provocation in contact dermatitis, but not for cADR. Because in contact dermatitis T cells at earlier positive patch tests can persist for some time, we hypothesised that homing of drug specific T-cells in the skin also plays a role in cADR, and was responsible for the localized flaring of earlier performed patch tests at desensitisation. Our observation also underlines that clinically negative patch tests a year after clinical recovery are no proof of the absence of a hypersensitivity mechanism.

Samenvatting van de hoofdstukken

Veiligheid, effectiviteit en kwaliteit van geneesmiddelen zijn aloude vraagstukken. Bijwerkingen van geneesmiddelen (BG), onlosmakelijk verbonden met medicamenteuze therapie, behoren tot de meest belangrijke oorzaken van iatrogene ziekten wat betreft morbiditeit en mortaliteit en zijn zo oud als de geneeskunde zelf. Daarnaast is vooral in de laatste decennia een verscheidenheid aan geheel nieuwe middelen geïntroduceerd, zoals de "targeted drugs" en "biologicals", die behalve nieuwe therapeutische mogelijkheden en een vebeterde kwaliteit van leven, naast de gebruikelijke BG ook een heel scala aan nieuwe en voorheen weinig voorkomende BG hebben geïntroduceerd.

De incidentie van BG is hoog, en zal naar verwachting in de toekomst niet afnemen onder invloed van de toenemende levensverwachting, mede gefaciliteerd door een groeiend gebruik van geneesmiddelen en toevoeging aan het arsenaal van steeds meer biofarmaceutica en andere nieuwe soorten geneesmiddelen. Polyfarmacie, veranderingen in het metabolisme en het verminderd functioneren van organen bij ouderen vormen risicofactoren voor BG, en het voorkomen of management van BG vormen daarmee dan ook een belangrijk vraagstuk bij het gezond oud worden ("healthy aging") en de kwaliteit van leven bij ouderen. Dit klemt temeer omdat de potentie tot het veroorzaken van BG door nieuwe middelen vaak pas ná de introductie van het middel op de markt aan het licht komt; enerzijds door de relatieve zeldzaamheid van veel van de BG ten opzichte van de premarketing geteste aantallen proefpersonen (enkele duizenden proefpersonen ten opzichte van relatieve risico's die lager kunnen zijn dan 1:1.000.000), anderzijds omdat premarketing in eerste instantie bij voorkeur "gezonde jonge mannen" worden getest en kwetsbare patiëntgroepen zoals baby's, zwangeren, vrouwen in de vruchtbare leeftijd, ouderen, en mensen met een reeds bestaande aandoening bij premarketing onderzoek vaak als proefpersoon worden uitgesloten.

Dermatologen worden regelmatig geconfronteerd met patiënten waarbij gedacht wordt dat zij mogelijk (muco)cutane oftewel huid-en/of slijmvliesafwijkingen hebben als reactie op geneesmiddelgebruik (cBG). Alhoewel nagenoeg elk middel cBG kan veroorzaken, is de kans hierop voor een individueel middel doorgaans laag. Behoudens uitzonderingen, weerspiegelt de hoge incidentie van cBG eerder de omvang van het geneesmiddelgebruik dan de reactiviteit van ieder middel op zich. Daarnaast kunnen cBG een zeer uiteenlopende verscheidenheid aan klinische en biologisch kenmerken vertonen die bovendien nog eens sterk kunnen lijken op andere ziektebeelden, inclusief idiopathische aandoeningen. De grote verscheidenheid aan cBG berust waarschijnlijk op verschillende pathomechanismen, die bovendien vaak niet of slechts ten dele zijn opgehelderd. Bovendien is het vaak niet eenvoudig het veroorzakende middel aan te wijzen, vooral wanneer sprake is van polyfarmacie. De grote klinische variabiliteit en heterogeniteit van cBG, in combinatie met de soms sterke gelijkenis met andere aandoeningen, kan gemakkelijk leiden tot een onjuiste diagnose. Zowel over- als onderdiagnose kan belangrijke gevolgen hebben, vooral wanneer sprake is van overgevoeligheidsreacties of allergie. Een

onterechte bestempeling als allergie heeft consequenties voor toekomstige therapeutische opties en kan resulteren in het onnodig uitwijken naar een duurdere en/of minder effectieve behandeling, terwijl het niet onderkennen van een allergische achtergrond kan resulteren in een soortgelijke of zelfs ernstiger reactie bij hergebruik van het veroorzakende middel.

De differentiaaldiagnostische overweging dat eventueel ook sprake zou kunnen zijn van een cBG is een premisse voor het onderkennen van een geneesmiddelgerelateerde aandoening, het reactietype en daarnaast het potentieel veroorzakende middel. Net als bij idiopatische aandoeningen, berust het onderscheid tussen de verschillende cBG vooral op de morfologie en distributie van de (muco)cutane afwijkingen. Een heldere definitie van de verschillende ziektebeelden die bij cBG kunnen optreden, kan helpen bij de herkenning van klinische patronen en daardoor bij het stellen van de diagnose, de daarop gebaseerde behandeling, de prognose en het veroorzakende middel.

Gelukkig zijn de meeste cBG mild en voorbijgaand. Behalve eventueel ondersteunende therapie is vroegtijdige herkenning, gevolgd door het prompt staken van het veroorzakende middel doorgaans voldoende om progressie van het beeld te voorkomen en volledige genezing te bewerkstelligen. Bij sommige ernstige vormen van cBG (severe cutaneous adverse ractions, ook wel afgekort als SCAR), kan echter aanvullend therapeutische interventie aangewezen zijn om de cascade van immunologische en nietimmunologische reacties, uitgelokt door de bijwerking, te blokkeren dan wel te matigen.

In dit proefschrift komen verschillende aspecten van classificatie en definitie van cBG, in het bijzonder van SCAR, de daarbij optredende differentiaal diagnostische overwegingen en therapeutische opties aan de orde. De focus ligt hierbij op Stevens-Johnson syndroom / toxisch epidermale necrolyse (SJS?TEN), acute gegeneraliseerde exanthemateuze pustulose (AGEP) en drug reaction with eosinophilia and systemic symptoms (DRESS).

Hoofdstuk 1 geeft een algemene inleiding over cBG en behandelt meer specifiek een aantal SCAR: SJS/TEN, AGEP, en DRESS. Hierbij wordt in het bijzonder ingegaan op de definitie, classificatie en afgrenzing van deze beelden, en daarnaast op recente kennis over de behandeling en pathogenese ervan.

De diversiteit van cBG is nagenoeg onbegrensd. Toch is het zinnig een duidelijk onderscheid te maken tussen de diverse beelden en niet het geheel als een continuüm te zien, indien dit een bijdrage kan leveren aan het vinden van originele klinische patronen met een eigen beloop, causaliteit, pathomechanisme, prognose en/of behandeling en de verantwoordelijke medicatie.

SCAR en enkele andere cBG zijn niet altijd uitsluitend beperkt tot de huid. Regelmatig "weerspiegelt" de huid als het ware bijwerking(en) die zich in andere organen afspelen. Het meest treffende voorbeeld hiervan is DRESS, waarbij naast een huidreactie tevens veelvuldig lymfadenopathie en hematologische afwijkingen kunnen voorkomen en vaak één of meerdere inwendige organen kunnen participeren. Bij andere SCAR zoals SJS/TEN en AGEP kan weliswaar ook systemische betrokkenheid optreden, maar de afwijkende mucocutane presentatie, in

combinatie met de mate van betrokkenheid van andere organen maakt het doorgaans mogelijk de diagnose te differentiëren.

In **hoofdstuk 2** wordt ingegaan op de controverse die bestaat rond de behandeling van SJS/TEN met corticosteroïden. Doel van de retrospectieve studie, die werd uitgevoerd in een kleine serie van 12 achtereenvolgens geïncludeerde patiënten met een gevalideerde diagnose van SJS/TEN, was het evalueren van de effectiviteit van een kortdurende puls therapie met hoge dosis dexamethason.

Naast orgaanfalen zijn infecties, waaronder sepsis, de belangrijkste oorzaak van de hoge mortaliteit bij SJS/TEN. Oorspronkelijk werden meestal corticosteroïden gepropageerd als behandeling voor SJS/TEN. Sinds het midden van de jaren 80 van de vorige eeuw echter, werd toepassing van corticosteroïden controversieel geacht en door sommige auteurs in reactie op enkele publicaties met negatieve uitkomsten zelfs als funest bestempeld. Daarna werd behandeling met andere middelen, zoals thalidomide, IVIG, of ciclosporine voorgesteld, maar een sluitend bewijs dat naast ondersteunende therapie ook specifieke behandeling een gunstig effect laat zien bij SJS/TEN, ontbreekt nog steeds. De enige uitgevoerde dubbelblinde, placebo gecontroleerde therapeutische studie bij SJS/TEN is die met thalidomide. Deze moest echter voortijdig worden afgebroken wegens oversterfte, waarna bij analyse bleek dat deze juist optrad in de actieve behandelingsarm. Resultaten van enkele ongecontroleerde studies van series patiënten die met intraveneus immuunglobuline (IVIG) werden behandeld zijn niet eenduidig en geven onvoldoende aanleiding IVIG als standaardtherapie aan te bevelen. Recent werden, hoewel niet significant, gunstige resultaten beschreven bij een open trial waarbij behandeling met ciclosporine plaatsvond.

Corticosteroïden hebben pleiomorfe immunomodulerende effecten, ondermeer door remming van diverse cytokines die vrijkomen bij SJS/TEN. Naar onze mening kunnen corticosteroïden een paradoxaal effect hebben op SJS/TEN. Te laat gestart en in een te lage dosis voortgezet tijdens het beloop van de aandoening kunnen zij via immunosuppressieve effecten infecties in de hand werken en mogelijk ook de wondheling vertragen. Daarentegen lijkt een aannemelijke basis aanwezig voor toepassing van een kortdurend hoge dosis in de acute beginfase van SJS/TEN. Daarbij kunnen zij potentieel immuunmechanismen blokkeren, die mede verantwoordelijk geacht worden voor de cascade die uiteindelijk leidt tot apoptose van keratinocyten, gevolgd door uitgebreide necrose en verlies van epidermis in SJS/TEN. In the uitgevoerde studie werd direct na het stellen van de diagnose SJS/TEN een hoge dosis dexamethason (1.5 mg/ kg lichaamsgewicht/ dag) gegeven als intraveneuze puls therapie op drie achtereenvolgende dagen. De uitkomsten van de studie ondersteunen de aanname dat kortdurende puls therapie met dexamethason, vroegtijdig gegeven in het acute proces, kan bijdragen aan verminderde mortaliteit bij SJS/TEN, zonder daarbij de duur van wondgenezing te verlengen.

Recente publicaties neigen er overigens toe minder negatief te zijn ten aanzien van corticosteroïden bij SJS/TEN, en een aantal auteurs onderschrijven het pleidooi voor een grotere multinationale studie naar het effect van een kortdurende, hoge dosis corticosteroïden bij SJS/TEN.

Hoofdstuk 3 laat de resultaten zien van een retrospectieve analyse van patiënten met SJS/TEN waarbij in de voorgeschiedenis op enigerlei wijze sprake was van lupus erythematosus (LE). De gegevens zijn ontleend aan een omvangrijke, op de gehele populatie gebaseerde nationale database van patiënten met een gevalideerde diagnose van SJS/TEN. Daarnaast werd tevens een review gegeven van de internationale literatuur over dit onderwerp. Hoofddoel van dit onderzoek was het vinden van differentiaal diagnostische verschillen tussen SJS/TEN en bulleuze vormen van LE, zowel op klinische als histopathologische gronden. Nevendoel was onderzoek naar de prevalentie van LE bij deze groep patiënten met SJS/TEN.

Van 1366 patiënten met SJS/TEN uit de onderzochte periode (1990 tot en met 2006) werden er 17 aangetroffen met een afdoende gedocumenteerde voorgeschiedenis van LE, waarvan tevens representatief histologisch materiaal van de huid ten tijde van de SJS/TEN beschikbaar was voor analyse. Bij negen van de 17 patiënten waren geen LE kenmerken gedocumenteerd kort voor of tijdens de periode met SJS/TEN; de andere acht daarentegen toonden klinisch en/of histopathologisch een aantal LE- kenmerken die tot een differentiaal diagnostische vraagstelling leidden. Nadere differentiatie kon worden gemaakt op basis van klinische en histopathologische gronden: vier van hen werden nader geclassificeerd als SJS/TEN met een voorafgaande LE uitbraak en/of LE-typische histopathologische kenmerken, terwijl de andere vier nader werden geduid als "TEN-like" LE.

SJS/TEN kan bij patiënten met LE optreden en bulleuze afwijkingen bij patiënten met LE hoeven niet per definitie te worden geïnterpreteerd als een manifestatie van LE. Daarbij zijn de meeste patiënten met SJS/TEN en een voorgeschiedenis van LE op grond van klinische en histopathologische kenmerken goed van elkaar te onderscheiden. In sommige gevallen kunnen de acute huidverschijnselen van LE en SJS/TEN echter fenotypisch sterke overeenkomsten vertonen, veroorzaakt door uitgebreide epidermale apoptose bij beide ziektebeelden. In deze gevallen kunnen in het bijzonder anamnese en klinisch beloop aanwijzingen geven voor het onderscheid tussen beide beelden. Ofschoon geen enkel kenmerk op zich doorslaggevend is, wijzen een combinatie van recente LE exacerbatie, uitgesproken fotodistributie, annulaire laesies en afwezigheid van palmoplantaire afwijkingen of afwezige of slechts milde, plaatselijke erosieve afwijkingen van de slijmvliezen klinisch eerder in de richting van LE dan op SJS/TEN. Histopathologisch wijzen in het bijzonder vacuolaire veranderingen, vooral op het grensvlak van epidermis en dermis, en matig tot dichte peri-adnexale en (diepe) perivasculaire lymfocytaire infiltraten eerder in de richting van LE.

Het relatief hoge aandeel patiënten met een voorgeschiedenis van LE in patiënten met SJS/TEN suggereert een verband tussen beide ziektebeelden, mogelijk doordat LE een risicofactor is voor SJS/TEN, dan wel dat beide een gezamenlijke risicofactor delen.

In **hoofdstuk 4 is** een studie opgenomen met de eerste systematische beschrijving van het histopathologische spectrum van AGEP, gebaseerd op een grote serie casus die werden ontleend aan 2 prospectieve multinationale studies. Alle geïncludeerde casus waren aan de hand van een algemeen aanvaard validatie score systeem gevalideerd als een waarschijnlijk of zeker geval van AGEP. Eerdere kennis betreffende de histopathologie van AGEP was hoofdzakelijk gebaseerd op case reports en enkele kleine klinische series. AGEP vertegenwoordigt een tamelijk zeldzaam, doorgaans geneesmiddel geïnduceerd reactie patroon, dat differentiaal diagnostisch onderscheiden moet worden van een aantal andere pustuleuze dermatosen. Doorslaggevende histopathologische kenmerken blijken superficiële spongiforme pustels, exocytose van neutrofiele granulocyten, necrotische keratinocyten, oedeem van de papillaire dermis, gemengdcellige dermale infiltraten die zich niet alleen superficieel maar ook dieper dermaal en interstitieel bevinden met neutrofiele en regelmatig ook eosinofiele granulocyten, en een doorgaans milde psoriasiforme epidermis. De diagnose kan worden gebaseerd op genoemde histopathologische kenmerken, in samenhang met klinische symptomen die op AGEP wijzen. Hieronder zijn te rekenen een acuut begin, koorts, neutrofilie, een kort beloop (≤ 15 dagen), verband met recent geïntroduceerde medicatie, spontaan herstel na staken van het mogelijk veroorzakende middel en het achterwege blijven van een recidief na genezing. De studie ondersteunt tevens het concept dat AGEP een aparte entiteit is die ook kan optreden bij patiënten met een voorgeschiedenis van psoriasis. Opmerkelijk was dat AGEP relatief vaker werd gezien bij patiënten met psoriasis in de voorgeschiedenis dan verwacht zou kunnen worden op basis van het voorkomen van psoriasis in de algemene bevolking.

In **hoofdstuk 5** wordt het spectrum van histopathologische kenmerken van een groep met als waarschijnlijk of zeker gevalideerde gevallen van AGEP vergeleken met gevallen van gegeneraliseerde pustuleuze psoriasis (GPP).

Differentiatie tussen AGEP en GPP, en in het bijzonder het acute stadium van het type van "von Zumbusch", vormt een klinische en histopathologische uitdaging. Van zowel AGEP als GPP werden stapsgewijze doorsneden van de huid, gekleurd met hematoxyline-eosine, systematisch geëvalueerd volgens identieke parameters en hun gradering. Ofschoon geen enkel histopathologisch kenmerk op zichzelf diagnostisch blijkt, kan de combinatie van kenmerken en hun gradering bijdragen aan het differentiëren van de diagnose. Kenmerken die wijzen op AGEP in plaats van op acute GPP zijn de aanwezigheid van eosinofielen in de pustels of dermis, necrotische keratinocyten, gemengde neutrofielrijke, interstitiële en diep middermale infiltraten, en het ontbreken van verwijde, kronkelige bloedvaten. Bij chronische GPP werden daarenboven significante epidermale psoriasiforme veranderingen aangetroffen,

terwijl zowel in acute als chronische GPP vaak verwijde, kronkelige en oppervlakkige vaten werden aangetroffen in de papillaire dermis. Deze histopathologische sleutelkenmerken, gecombineerd met een clinicopathologische correlatie, zal in de meeste gevallen kunnen bijdragen aan de differentiatie tussen AGEP en GPP.

Deze studie ondersteunt tevens dat AGEP niet een variant is van pustuleuze psoriasis, maar een afzonderlijke entiteit vertegenwoordigt. Ook werd in deze studie de eerdere suggestie dat AGEP proportioneel vaker voorkomt in patiënten met psoriasis ten opzichte van de algehele bevolking, bevestigd.

In **de hoofdstukken 6a en 6b** worden twee gevallen van AGEP beschreven, die konden worden toegeschreven aan morfinehydrochloride respectievelijk morfinesulfaat. Morfine heeft wat betreft cBG een relatief veilig profiel, en werd niet eerder beschreven als middel dat AGEP kan veroorzaken.

Morfine wordt regelmatig kortdurend postoperatief verstrekt, terwijl het middel daarnaast ook wel langduriger wordt gegeven, bijvoorbeeld ter verlichting van ernstige chronische pijn. Vooral in de postoperatieve periode, zoals bij onze eerste casus, kunnen symptomen als koorts, erytheem en pustels makkelijk worden toegeschreven aan andere oorzaken zoals infectie. Bovendien kunnen de soms slechts speldenknop grote pustels licht over het hoofd worden gezien. Omdat AGEP spontaan en meestal vrij snel geneest na staken van het veroorzakende middel kan de reactie, vooral bij een korte toedieningduur, gemakkelijk gemist worden als zijnde geneesmiddelgerelateerd. Na afloop van de reactie werd morfine als oorzakelijk middel bevestigd door positieve plakproeven en een positieve lymfocytentransformatietest.

In **hoofdstuk 6b** wordt een tweede geval beschreven, waarbij onder andere morfinesulfaat werd gegeven wegens ernstige rugpijn. Complicerend in deze casus, die klinisch gelijkenis toonde met TEN, was een voorgeschiedenis van psoriasis en een mogelijk eerder doorgemaakte SCAR. Dit noodzaakte tot differentiatie van AGEP met GPP en TEN. De histopathologie met spongiforme subcorneale pustels en gemengde perivasculaire en interstitiële dermale infiltraten, in combinatie met een spoedige genezing zonder recidief na staken gaf aanleiding tot de diagnose AGEP. De rol van morfine als oorzaak van de reactie werd later bevestigd door de uitkomsten van aanvullend epicutaan allergologisch onderzoek. Beide casus demonstreren dat cBG altijd in de diagnostische overweging moet worden meegenomen. Dit geldt temeer bij onverklaarbare symptomen, zelfs als het betreffende middel niet eerder als veroorzaker werd beschreven.

Positieve in vitro en/of in vivo testen kunnen helpen bij het vaststellen van een geneesmiddel gerelateerde etiologie en het veroorzakende middel aanwijzen. Opmerkelijk was dat de positieve, pustuleuze plakproef bij de tweede casus de oorspronkelijke huidreactie weerspiegelde. De positieve in vivo en in vitro testen bij AGEP onderschrijven voorts dat AGEP

een vertraagde overgevoeligheidsreactie is, waarbij naast neutrofiele granulocyten ook T-cellen zijn betrokken.

In **hoofdstuk 7** worden twee patiënten gepresenteerd met "symmetrical drug-related intertriginous and flexural exanthema" (SDRIFE), eerder ook wel bekend als het "baboon syndrome". De reactie werd in beide gevallen veroorzaakt door omeprazol, een potente, veelvuldig gebruikte en doorgaans goed getolereerde proton pomp remmer, welke niet eerder expliciet werd gemeld als veroorzaker van SDRIFE.

Diagnostische criteria voor SDRIFE zijn, behalve systemisch geneesmiddelengebruik, een scherp begrensd erytheem van het gluteale/perianale gebied en/of een V-vormig erytheem van het inguinale/perigenitale gebied, betrokkenheid van tenminste één andere intertrigineuze plooi waarbij sprake is van een symmetrische verdeling en het afwezig zijn van systemische betrokkenheid. Ofschoon de distributie en overige kenmerken van de huidafwijkingen bij beide casus typisch waren voor SDRIFE, werden daarenboven enkele nogal ongebruikelijke kenmerken waargenomen zoals pustels, betrokkenheid van andere huidplooien, geringe systemische betrokkenheid, waaronder neutrofilie en eosinofilie in het bloedbeeld, en een langer dan doorgaans gemelde latentietijd voor het ontstaan van de afwijkingen na introductie van het veroorzakende middel. Behalve de lokalisatie van de afwijkingen in de flexuren noopten vooral de aanwezigheid van pustels, de uitgebreidere distributie dan voor SDRIFE gebruikelijk is, en de milde systemische verschijnselen tot differentiatie met AGEP.

In **hoofdstuk 8,** worden twee patiënten beschreven die na behandeling met erlotinib (Tarceva®) wegens kleincellig longcarcinoom langdurig uitgebreide acneïforme huidafwijkingen en een droge huid ontwikkelden. Dit droeg ertoe bij dat zij meer vatbaar waren voor infectie, resulterend in uitgebreide en invaliderende secundaire impetiginisatie. Omdat bij beiden een uitgebreide pustuleuze rash ontstond, bij één van hen geprononceerd aanwezig in de plooien en gepaard met koorts, werd tevens AGEP overwogen.

Erlotinib is een EGFR remmer, behorend tot de nieuwe klasse van "molecular targeted drugs". Targeted drugs worden in toenemende mate ingezet, in het bijzonder bij therapieresistentie voor conventionele chemotherapeutica, en hiermee vergeleken, combineert erlotinib een hoge effectiviteit tegen solide tumoren met een geringere systemische toxiciteit. Keerzijde is het vaak optreden van nevenwerkingen, die aanzienlijk ongemak en morbiditeit kunnen veroorzaken. Targeted drugs kunnen bovendien, naast de alom bekende bijwerkingen, ook ongebruikelijke reacties teweeg brengen die tamelijk afwijken van die welke bij conventionele geneesmiddelen kunnen worden gezien. De vaak voorkomende acneïforme erupties door erlotinib berusten op de farmacologische eigenschappen van het middel, zijn klasse gebonden en dosis gerelateerd, en worden daarmee tot de veelvoorkomende zogenaamde Type A reacties gerekend. Aangezien de ernst van de acneïforme erupties blijkt te correleren met de effectiviteit van de bedoelde werking van erlotinib tegen de tumor, is bekendheid met het voorkomen van dit type reacties

en een proactieve benadering van de behandeling ervan gewenst. Tijdige dermatologische interventie kan de effecten van deze nevenwerking matigen, voortzetting van de therapie mogelijk maken en dientengevolge aanzienlijk bijdragen aan de kwaliteit van leven.

Het pathomechanisme van deze pustuleuze, zogenaamd acneïforme reactie is voorshands nog onvoldoende bekend, maar het wijst in de richting van een disbalans tussen de rijping en proliferatie van keratinocyten. Het kan leiden tot een verdund stratum corneum en ontsteking met aantasting van de haarfollikels. Deze raken hierdoor verwijd en gevuld met overmatig keratine, soms bovendien gevolgd door secundaire infectie.

In **hoofdstuk 9a** worden de definitie en kenmerken van DRESS behandeld, opgesteld op basis van literatuuronderzoek, pilotstudies en consensusbijeenkomsten van een multidisciplinaire groep experts, voornamelijk afkomstig uit Europa. Er lijkt een duidelijk tendens waarneembaar dat deze definitie en kenmerken ook door andere groepen onderzoekers worden overgenomen.

Reeds in 1950 rapporteerden zowel Welton als Chaiken *et al.* onafhankelijk van elkaar een geval van een ernstige reactie met huidverschijnselen en betrokkenheid van inwendige organen, veroorzaakt door de chemisch verwante middelen phenobarbital respectievelijk phenytoine (Dilantin®). Vervolgens is voor deze en enkele andere medicijnen herhaaldelijk een syndroom gemeld in de literatuur, gekenmerkt door de trias koorts, huidreactie en betrokkenheid van interne organen. Dit syndroom werd een grote verscheidenheid aan namen en acroniemen aangeduid, hetzij gerelateerd aan het gebruikte middel ("anticonvulsant hypersensitivity syndrome"), hetzij aan het meest aangedane orgaan of het ziektebeeld dat werd geïmiteerd ("mononucleosis-like syndrome"), dan wel aan de veronderstelde pathogenese ("drug hypersensitivity syndrome", of HSS). De in het verleden frequent gehanteerde benaming "hypersensitivity syndrome" is evenwel tamelijk aspecifiek, en voor meerderlei uitleg vatbaar, kan aanleiding geven tot verwarring en is minder geschikt om onderscheidende kenmerken weer te geven. Dit heeft er ondermeer toe geleid dat soms gevallen van SJS/TEN, AGEP, en zelfs milde cBG waarbij enige systemische betrokkenheid optrad, werden aangemerkt als HSS. Tevens heeft dit geresulteerd in het ten onrechte bestempelen van SJS/TEN als een variant van HSS en melding van elkaar overlappende entiteiten. Dit gaf aanleiding tot introductie van het meer informatieve en betekenisvolle acronym DRESS (drug reaction with eosinophilia and systemic symptoms), dat in toenemende mate wordt gebruikt om het syndroom aan te duiden.

Teneinde een homogeen cohort van patiënten met het syndroom te kunnen verzamelen voor verder onderzoek, en omdat bovendien een eenduidige definitie en beschrijving van de kenmerken van DRESS ontbraken, werd een diagnostisch score systeem ontwikkeld voor de validatie van potentiële gevallen, waarbij tevens de mate van waarschijnlijkheid kon worden weergegeven (zeker, waarschijnlijk, mogelijk, of geen geval).

In **hoofdstuk 10** is een studie opgenomen met de analyse van de eerste prospectieve multicenter studie van 117 gevallen, gevalideerd als zekere of waarschijnlijke DRESS, volgens het nieuwe

bovengenoemde diagnostisch validatie score systeem. Aangezien aanmelding en inclusie van de patiënten onafhankelijk waren van de uitkomst en blootstelling aan bepaalde medicatie of andere risicofactoren, kunnen de resultaten van deze studie als mogelijk minder bevooroordeeld worden beschouwd, vergeleken met die van eerdere, retrospectieve series. Bovendien draagt verzameling door getrainde interviewers van gegevens via directe interviews met patiënten en zorgverleners onder gebruikmaking van voor de aandoening specifieke vragenlijsten, gevolgd door een systematische en gestructureerde validatie door een "expert comittee" bij aan de sterkte van de studie. De validatie vond plaats op basis van foto's en gestructureerde gegevens betreffende beloop, klinische en biologische parameters, en histopathologisch onderzoek, doch geblindeerd voor de gebruikte medicatie en andere risicofactoren. Afwijkende bevindingen worden, indien zij kunnen worden toegeschreven aan een alternatieve oorzaak, uitgesloten bij de validatie als DRESS.

Behoudens bevestiging van het tamelijk variabele karakter van DRESS, met een veelvoud aan combinaties van symptomen en afwijkende laboratorium en andere onderzoeksgegevens, ook qua mate van ernst, een geleidelijk begin na start medicatie en een langer aanhoudend ziektebeloop vergeleken met andere cBG, waren nieuwe bevindingen een vrouwelijke predominantie, de significant jongere leeftijd van vrouwen, en het vaker voorkomen van milde slijmvliesafwijkingen, eosinofilie en atypische lymfocyten in het perifere bloed en een lagere mortaliteit dan doorgaans gemeld. Daarnaast vond beschrijving plaats van de prodromale verschijnselen, die optreden voordat mucocutane of andere afwijkingen gezien worden. Ondanks blindering voor geneesmiddelgebruik bij inclusie en validatie bleek het spectrum van verantwoordelijke middelen relatief beperkt, met aromatische antiepileptica en allopurinol als de belangrijkste veroorzakers. Geruststellend was dat toepassing van het nieuwe diagnostische validatie score systeem slechts nauwelijks leidde tot overlap met SJS/TEN en AGEP. De bevindingen bevestigen dat DRESS een origineel fenotype vertegenwoordigt binnen de groep van SCAR wat betreft klinische en biologische kenmerken, veroorzakende middelen, latentietijd en beloop.

In **hoofdstuk 11** wordt een interessante observatie gemeld die werd waargenomen tijdens een desensitisatie procedure met trimethoprim-sulfamethoxazole (co-trimoxazol), verricht vanwege een eerdere ernstige cBG op dit middel bij een HIV-positieve patiënt. Ongeveer een jaar na de oorspronkelijke reactie werden plakproeven met cotrimoxazol verricht. De uitkomsten werden als zwak positief beoordeeld en, bij herhaling van de test, als negatief. Vrijwel aansluitend werd de desensitisatie procedure gestart. Enkele uren na de laatste desensitisatie stap (dag drie) ontwikkelde patiënt erytheem, beperkt tot de lokalisaties van de eerdere zwak positieve en negatieve plakproeven, in combinatie met voorbijgaande koorts, malaise, een verhoogd C-reactief proteïne en perifere eosinofilie. Het fenomeen van het opvlammen van eerdere plakproeven is voorheen beschreven voor nikkel en goud na systemische provocatie bij contacteczeem, maar niet eerder voor cBG. Naar analogie van contacteczeem waarbij T cellen

gedurende enige tijd aanwezig blijven op plaatsen van een eerder verrichte plakproef, werd door ons gepostuleerd dat "homing" van geneesmiddelspecifieke T cellen in de huid ook een rol speelt bij cBG, en dat dit fenomeen verantwoordelijk was voor het plaatselijk opvlammen van de reactie op de lokalisaties waar op een eerder tijdstip plakproeven met het geneesmiddel waren verricht. Onze bevinding onderstreept ook dat klinisch negatief bevonden plakproeven geen absoluut bewijs zijn voor de afwezigheid van een eerdere overgevoeligheids reactie.

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ADDENDUM

Dankwoord / Acknowledgements
Bibliography
Curriculum Vitae

Dankwoord/Acknowledgements

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voor behandeling op onze kliniek. Dit heeft uiteindelijk geresulteerd in het "Groninger TEN protocol" dat inmiddels ook in een aantal andere ziekenhuizen wordt gehanteerd.

Professor dr. J.G.R. de Monchy, beste Jan. Samen met jouw afdeling Allergologie hebben we het multidisciplinair spreekuur toxicodermie opgezet. Daarnaast hebben we vormgegeven aan het onderwijs toxicodermie aan co-assistenten, scholing van AIOS Interne geneeskunde en een aantal sessies voor het ochtendrapport van de internisten. Ook heb je meegeschreven aan twee artikelen die in dit proefschrift zijn opgenomen. Je bent een geboren docent, bent bij uitstek iemand die `out of the box` kan denken en vooral je enthousiasme en positieve en collegiale instelling heb ik altijd als heel plezierig ervaren. Dank hiervoor.

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Professor dr. A.C. van Grootheest, beste Kees. In jouw persoon wil ik ook alle andere medewerkers van Lareb en medeleden van de Wetenschappelijke Advies Raad van Lareb bedanken voor de stimulerende samenwerking op het gebied van pharmacovigilantie in Nederland. Vooral de multidisciplinaire samenstelling van de adviesraad geeft iedere keer weer grond voor geanimeerde discussies.

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Ik ken jullie vanaf mijn vroegste studietijd in Groningen toen ik met jullie Duits studeerde. Behalve dat we elkaar regelmatig zagen vanwege de gemeenschappelijke studie werden we al gauw vrienden. Hoewel we uiteindelijk alle drie een andere richting zijn opgegaan, hebben we door de jaren heen contact gehouden en lief en leed met elkaar gedeeld. Naast de tussentijdse contacten is het jaarlijks etentje met ons drietjes in het Groninger museum steeds weer een moment van bijkomen en lekker bijpraten. Ik ben dan ook blij dat jullie tijdens een van deze etentjes toezegden mijn paranimfen te willen zijn en mij te helpen met de organisatie rond de dag van de promotie.

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Over de auteur

Sylvia Kardaun werd geboren op 4 juli 1950 in Heerlen. Na het behalen van het HBS A diploma en de MO akte Duits met onderwijsbevoegdheid keerde zij terug naar haar oude middelbare school voor het halen van het Atheneum B diploma in verband met de wens geneeskunde te gaan studeren. Tijdens deze studie werkte ze anderhalf jaar op het laboratorium klinische chemie op de Bloemsingel Groningen, eerst als practicum assistent en vervolgens als onderzoeker naar de effecten op de hematopoeise van een voor chlooramphenicol vervangend middel.

Na afronding van de studie geneeskunde in 1978 was ze werkzaam als AIOS Interne Geneeskunde in Enschede en verrichtte ze onderzoek naar ANA subtyperingen.

In 1980 ving haar opleiding tot dermatoloog in Leiden aan, welke in 1984 werd afgerond. Tijdens haar specialisatie verrichte ze onderzoek naar geneesmiddelbijwerkingen, resulterend in enkele publicaties.

Aansluitend aan haar specialisatie als dermatoloog werd zij in 1984 benoemd tot staflid op de afdeling Dermatologie van het latere Universitair Medisch Centrum Groningen met naast de algemene dermatologie als speciaal aandachtsgebied de dermatopathologie, inclusief de verantwoordelijkheid voor het dermatopathologisch laboratorium dat destijds nog onder de afdeling Dermatologie viel. Na overgang van het dermatopathologisch laboratorium naar de afdeling Pathologie verschoof het accent naar klinische en poliklinische werkzaamheden.

Met de komst van Professor Jan van der Meer naar Groningen begin jaren negentig ontstonden, door een wederzijdse belangstelling voor SJS/TEN geleidelijk aan opnieuw mogelijkheden voor onderzoek naar geneesmiddelbijwerkingen op de huid. Dit werd gevolgd door aansluiting bij de multinationale RegiSCAR studiegroep in 2002, het verrichten van reviews voor cutane bijwerkingen voor de WHO-UMC in Uppsala vanaf 2003, toetreding tot de Wetenschappelijke Advies Raad van het bureau landelijke registratie bijwerkingen Nederland (Lareb) in 2006, toekenning van de topreferente functie voor toxicodermie aan de afdeling Dermatologie van het UMCG in 2007 en een aantal onderzoeken en publicaties over dit onderwerp.

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